Clinical practice guidelines for the care and treatment of breast cancer:

8. Adjuvant systemic therapy for women with node-positive breast cancer (2001 update)

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*The Steering Committee is part of Health Canada's Canadian Breast Cancer Initiative.

Abstract

Objective: To facilitate the choice of systemic adjuvant therapy for women with node-positive breast cancer.

Evidence: Based on systematic literature review using MEDLINE from 1976 and CANCERLIT from 1983 to May 2000. Nonsystematic review of literature was continued through January 2001.

Recommendations:

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 individually 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.

Validation: The authors' original text was revised by a writing committee, primary and secondary reviewers, and by the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. The final document reflects a consensus of all these contributors. External validation of the 1998 guideline was through the *CMAJ* review process; the current update did not require external review. A writing committee updated the original guideline and then submitted it for further review, revision and approval by the Steering Committee.

Sponsor: The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer was convened by Health Canada.

Completion date: January 2001.

Approximately 50% of patients with palpable breast cancer will prove to have axillary lymph-node involvement at surgery (pathologic stage II).<1> These women are at high risk of subsequent systemic relapse and death from metastatic breast cancer, even though investigations done at the time of diagnosis, such as routine blood counts, liver function tests and chest radiographic examinations, may reveal no evidence of cancer.

Before the advent of adjuvant systemic therapy, the 10-year survival for patients with axillary lymph-node involvement ranged from 25% to 48%.<2–6> Patients with 1 to 3 positive nodes had a 10-year survival of approximately 40% to 60%, and patients who had 4 or more involved lymph nodes had a 10-year survival of approximately 25%.<3–6>

Intervention with anticancer chemotherapy or hormonal therapy has been studied extensively over the past 25 years. Adjuvant systemic therapy with the use of multidrug chemotherapy or hormone therapy has been shown to prolong disease-free and overall survival among patients with stage II breast cancer, both in randomized clinical trials<7–17> and in population-based studies.<18> However, many women still succumb to progressive breast cancer, and there are many unanswered questions about how best to plan optimal adjuvant systemic treatment.

Recommendations for pre- and postmenopausal women are grouped separately. Premenopausal women are defined as all women whose last menstrual period was within 12 months before the diagnosis of breast cancer. Also, age less than 50 years has been used as a surrogate for premenopausal status.<11> “Adjuvant systemic therapy” refers to the use of cytotoxic drugs (chemotherapy), endocrine manipulation by ovarian ablation or use of drugs such as tamoxifen (hormonal therapy).

Method

The authors conducted a systematic review of the published literature retrieved from MEDLINE (1976 to May 2000) and CANCERLIT (1983 to May 2000). The terms used were “breast neoplasms,” “invasive breast adenocarcinoma,” “adjuvant,” “chemotherapy,” “hormonal

therapy," "premenopausal node-positive," "postmenopausal node-positive," "randomized studies," and "high doses." The search was restricted to English-language articles. Additional articles were identified by reviewing references in retrieved reports. Nonsystematic review of the literature was continued through January 2001. The quality of the evidence on which conclusions were based was categorized into 5 levels (see Levels of Evidence).<19> The iterative process used to develop this guideline has been described previously.<20> A writing committee updated the original guideline and then submitted it for further review, revision, and approval by the Steering Committee.

Recommendations (including evidence and rationale)

Premenopausal women

Adjuvant chemotherapy

- **Chemotherapy should be offered to all premenopausal women with stage II breast cancer.**

Chemotherapy has been shown to prolong recurrence-free and overall survival among premenopausal patients with stage II breast cancer, both in randomized clinical trials (level I evidence)<7–16> and in population-based studies (level III evidence).<18> The Early Breast Cancer Trialists' Collaborative Group recently updated their meta-analysis, often called the "Overview analysis" of 47 trials of chemotherapy in women with early breast cancer.<16> There was a proportional risk reduction of 34% in recurrence among women under 50 years who received polychemotherapy compared with those who received no treatment; the corresponding risk reduction in mortality was 27%. At 10 years there were absolute differences of 15.4% in recurrence and 12.4% in survival in favour of chemotherapy. The benefit of chemotherapy was observed in both women with estrogen receptor (ER)-positive tumours and those with ER-negative tumours.

A proportional reduction in risk applies uniformly to patients with varying risk factors. However,

the absolute benefit increases with the extent of lymph-node involvement, since the underlying base rates of recurrence and mortality increase with increasing lymph-node involvement.

The subanalyses of patients given chemotherapy indicated that prolonged polychemotherapy, usually with cyclophosphamide, methotrexate and 5-fluorouracil (CMF), was more effective than brief pre- or perioperative chemotherapy. The data in the Overview analysis did not answer the question of whether prolonged chemotherapy should begin before or after surgery. However, results of recent trials have failed to detect a difference in disease-free survival and overall survival between chemotherapy administered preoperatively and that commenced after surgery.<21>

Prolonged polychemotherapy was, in general, better than prolonged single-agent therapy. Prolonged CMF-type polychemotherapy for 12 to 24 months did not prove to be superior to shorter regimens, such as a 6-month course of CMF.

In addition to influencing survival, there is level III evidence based on a retrospective case review that chemotherapy may also significantly reduce the rate of local recurrence among patients who have undergone breast-conserving surgery followed by radiotherapy.<18>

- **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 individually choose to this treatment. Participation in approved clinical trials should be strongly encouraged.**

Most patients in the earlier Overview analyses were treated with CMF.<11,16> A variety of CMF variants were reported, including both oral and intravenous cyclophosphamide regimens. In general, most of the regimens lasted 12 months, since these were early studies carried out before 1985.

In the recent Overview analysis, the results of 11 trials that compared anthracycline-containing regimens with CMF were analyzed.<16> The anthracycline-containing regimens were associated with a proportional reduction of 12% in recurrence and of 11% in mortality compared with CMF regimens. One of the trials in this analysis was the MA5 trial conducted by the National Cancer Institute of Canada Clinical Trials Group. In this trial, over 700 premenopausal women with node-positive breast cancer received either CEF or CMF. There was a statistically significant improvement in relapse-free survival and overall survival in favour of CEF at a median follow-up of 60 months (level I evidence).<22> The improvement in relapse-free survival and overall survival of epirubicin-containing adjuvant chemotherapy regimens over CMF was recently supported by the results of a large trial conducted by the Danish Cooperative Group.<23>

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-15 study compared 4 cycles of AC administered every 3 weeks for 2 to 3 months with 6 cycles of CMF.<24> No difference in outcome was detectable at 3 years, which demonstrated that a 2- to 3-month course of AC is equivalent to a 6-month course of oral CMF (level I evidence).

The InterGroup recently reported the preliminary results of a trial that used a factorial design to compare three different doses of doxorubicin in AC (60, 75 and 90 mg/m^2) and compared AC for 4 cycles with AC followed by paclitaxel (175 mg/m^2) administered every 3 weeks for 4 cycles.<25> Patients with ER-positive tumours received tamoxifen for 5 years. A total of 3170 pre- and postmenopausal women with node-positive breast cancer were entered, and the median follow-up was 30 months. There was no difference detected between the 3 doses of doxorubicin, but the addition of paclitaxel to AC was associated with a risk reduction of 22% in recurrence (hazard ratio = 0.78, 95% confidence interval [CI] 0.67–0.91) and 26% in mortality (hazard ratio

= 0.74, 95% CI 0.60–0.92) (level I evidence). The benefit however, appeared to be confined to the patients with ER-negative tumours. The hazard ratio for disease-free survival among the 2066 patients with ER-positive cancer was 0.92 (95% CI 0.73–1.16), and among the 1055 patients with ER-negative cancer it was 0.68 (95% CI 0.55–0.85). It is possible that with longer follow-up a benefit may be detected among the patients with ER-positive disease. The data were recently updated at the National Institutes of Health (NIH) Consensus Conference.<26> At a median follow-up of 52 months, the reduction in hazard rates for recurrence and mortality were 13% and 14% respectively. The additional benefit of paclitaxel continued to be observed only in patients with ER-negative tumours.

At the NIH Consensus Conference, early results of the NSABP B-28 trial were presented.<26> Women with node-positive breast cancer were randomly assigned to receive either AC alone for 4 cycles or AC followed by paclitaxel (225 mg/m^2) every 3 weeks for 4 cycles. Tamoxifen was given to all women over 50 years of age and to those under 50 with ER-positive or progesterone receptor (PR)-positive tumours. Over 80% of the women received tamoxifen. The median follow-up was 34 months. There have been 282 events in the 1529 patients in the AC group compared with 269 events in the 1531 women who received AC followed by paclitaxel. This difference corresponds to a relative risk of 0.93 (95% CI 0.78–1.1, p = 0.38). There have been 133 deaths in the AC group compared with 136 in the AC followed by paclitaxel group (relative risk 1.0; 95% CI 0.78–1.27, p = 0.98). No statistically significant differences in outcomes were detected between patients who received tamoxifen and those who did not. There have been 5 cases of acute leukemia or myelodysplastic syndrome in the AC followed by paclitaxel group compared with none in the AC group.

The Cancer and Leukemia Group B (CALGB) trial reported a difference in recurrence and mortality very early on in the trial.<25,26> On subgroup analysis, this effect appeared to be in the group of patients with ER-negative tumours. With longer follow-up, there was still a reduction in recurrence and mortality, but of a smaller magnitude. The NSABP trial has so far failed to detect a difference. The follow-up has been much shorter than that in the CALGB trial.

Because a large proportion of the women in the NSABP trial received tamoxifen, this could make it more difficult to detect a difference in terms of power, and thus a longer follow-up is required.

The NIH Consensus Conference panel made the following statement concerning taxanes: "Although a number of such trials have completed accrual and others remain in progress, currently available data are inconclusive and do not permit definitive recommendations regarding the impact of taxanes on either relapse-free or overall survival. There is no evidence to support the use of taxanes in node negative cancer outside the setting of a clinical trial."<26>

- **Potential toxic effects of chemotherapy should be fully discussed with patients.**

A major factor in the choice between adjuvant chemotherapy regimens is the patient's quality of life. Some fatigue is common with all chemotherapy regimens. Patients may prefer to take the brief, 3-month AC regimens rather than the 6-month CMF program with the aim of having a briefer period of side effects and reducing disruption of their normal working and family lives.

CMF frequently causes mild to moderate nausea and vomiting.<27> These symptoms are usually transient and can be effectively controlled with medication. With respect to oral CMF, chemotherapy is administered for 84 days over a 6-month period, so nausea may be more protracted. Four cycles of intravenous AC (1 every 3 weeks) may cause more severe but briefer nausea and vomiting.<24>

AC and CEF cause complete but temporary hair loss; oral CMF causes some hair loss in 70% of patients and severe loss in 40%. Each of these regimens may cause mild, transient irritation of the mucous membranes of the mouth, throat and eyes and, rarely, chemical cystitis.<28>

All regimens cause transient myelosuppression, and there is an increased risk of infection, which, fortunately, is uncommon.<27> Fatal toxicity in the Early Breast Cancer Trialists' Collaborative Group reports varied from 0.1% to 1.0%.<11> Anthracycline-containing chemotherapy is limited

by severe dose-related cardiotoxicity. With doxorubicin, toxicity presenting as heart failure is uncommon (± 1%) when the total cumulative dose is kept below 300 mg/m^2.<29,30> The frequency of toxicity increases with increasing dose and age of the patient. Epirubicin likewise causes heart failure at higher doses but only very rarely (approximately 1%) at cumulative doses below 1000 mg/m^2.<31> Cardiac damage, when it occurs, is not rapidly reversible.<32> Ovarian failure causing an early menopause is common, especially in older premenopausal patients. Weight gain during treatment may occur in 14% of patients receiving CMF regimens.<28> Follow-up of patients receiving standard CMF regimens has not revealed a significant increase in drug-induced neoplasms.<33,34> The occurrence of leukemia was extremely rare in patients treated with CMF at the Milan Cancer Institute.<35> However, a worrisome incidence of acute nonlymphocytic leukemia (as high as 1% in some studies) has been reported after the use of combinations of anthracyclines and alkylating agents.<22,36,37> Paclitaxel can be associated with myelosuppression and alopecia. It also has its own unique toxicities, including hypersensitivity reactions, peripheral neuropathies, myalgias and arthralgias.

The choice of CEF over CMF and the choice of AC followed by paclitaxel over AC alone involves the patient weighing the incremental improvements in disease-free survival and overall survival against the increase in side effects.

- **Systemic adjuvant chemotherapy should begin as soon as possible after the surgical incision has healed.**

The NSABP conducted a trial that showed no difference in survival between women given chemotherapy preoperatively (neo-adjuvant) and those given chemotherapy postoperatively (level I evidence).<21> On the other hand, Colleoni and associates examined the relation between outcome and time to initiation of adjuvant chemotherapy in premenopausal women in a series of International Breast Cancer Study Group trials (level V evidence).<38> Among women with ER-negative tumours, the 10-year disease-free survival was 60% when chemotherapy was started within 21 days after surgery compared with 34% when treatment was started after 21 days ($p < 0.01$). No difference was observed among patients with ER-positive tumours.

Current practice is guided by the presumption that a prolonged delay is not in the best interest of the patient. Most clinical trials have insisted on the initiation of therapy within 12 weeks after surgery. In practice, most women begin treatment 4 to 6 weeks after their surgery. For patients who are candidates for radiotherapy, the optimal sequencing of chemotherapy and irradiation has not been defined. Most centres administer chemotherapy first. Some administer both concurrently, but this may increase the chance of toxic effects, especially when an anthracycline-containing regimen is used (level III evidence). This issue is considered in guideline 6.

- **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.**

CMF regimens of 6 months' duration are as effective as longer regimens of 12 to 24 months (level I evidence).<39> The NSABP B-15 study demonstrated that 4 cycles of intravenous AC at 3-week intervals was equivalent to 6 cycles of oral CMF at 4-week intervals (level I evidence).<24>

An early study from the Dana-Farber Cancer Clinic that compared 5 cycles of AC (15 weeks) to 10 cycles of AC (30 weeks) in patients with node-positive breast cancer did not detect any

differences at 9 years.<40> The Eastern Cooperative Oncology Group compared 4 months of CMF plus prednisone and tamoxifen (CMFPT) with 12 months of the same chemotherapy in postmenopausal patients and found no difference.<11> However, this last result may be attributable to the lack of much benefit from CMF in postmenopausal patients who also receive adjuvant tamoxifen. In contrast, the Ontario Clinical Oncology Group compared a 12-week regimen of CMF plus vincristine and prednisone (CMFVP) plus doxorubicin and concurrent tamoxifen with a 36-week regimen of CMFVP in node-positive patients, and reported increased relapse-free and overall survival among patients taking the longer-duration treatment.<41> Although this is classified as level I evidence, both the duration of therapy and the chemotherapy regimens differed, making it difficult to determine which factor influenced the outcome.

The International Breast Cancer Study Group, using a factorial design, randomly assigned premenopausal women with node-positive breast cancer to 6 cycles of CMF, 6 cycles of CMF plus 3 courses of re-induction CMF, 3 cycles of CMF, or 3 cycles of CMF followed by 3 courses of re-induction CMF.<42> Patients who received 3 cycles of CMF had a statistically significant reduction in disease-free survival (level I evidence). The German Breast Cancer Study Group used a factorial design to evaluate duration of chemotherapy (6 cycles of CMF versus 3 cycles of CMF) and tamoxifen in 481 patients.<43> No difference was detected between the 2 groups of patients (level II evidence).

Based on the results of the trials by the Ontario Clinical Oncology Group and the International Breast Cancer Study Group, 3 months of CMF cannot be recommended.

- **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.**

There has been no randomized comparison between intravenously and orally administered cyclophosphamide when used as adjuvant therapy. A European study (EORTC) that compared these regimens in patients with metastases demonstrated a higher response rate, better duration of

response and longer survival in those receiving oral rather than intravenous CMF (level II evidence).<44> It should be noted, however, that the oral regimen was more dose-intensive.

- **When possible, patients should receive the full standard dosage. High-dose chemotherapy with stem-cell support is not recommended.**

Dose intensity has been addressed in a trial by the Cancer and Leukemia Group B (CALGB), involving 1572 women, half of whom were premenopausal.<45,46> This trial compared 3 different dose regimens of 4 to 6 courses of CAF. It showed that the moderate- and high-dose regimens were more effective than the low-dose regimen, but also that there was no difference between the 2 higher doses (level I evidence). However, even the highest dose regimen in this study is comparable to conventional CAF chemotherapy and does not, in fact, represent a true "high-dose" regimen. This study suggests, therefore, that there is a threshold dose effect, below which chemotherapy is less effective and above which no further benefit is obtained. The results should be interpreted as indicating that, when possible, patients should receive the full dosage of their standard regimen, since there may be some erosion of benefit at lower doses. The study should not be interpreted to indicate that a higher dose intensity will necessarily convey an additional benefit.

This is consistent with the findings reported by Bonadonna and Valagussa in 1981.<47> In this landmark study, 20 years of follow-up of 386 women (half of whom were premenopausal) who received oral CMF showed that only those who received at least 85% of the planned dose benefited from adjuvant chemotherapy (level I evidence). These data tend to support delivery of full doses, when possible. Similarly, in a trial conducted in France involving women with node-positive cancer given either FEC (100 mg epirubicin) or FEC (50 mg epirubicin) every 3 weeks, the regimen with the higher dose of epirubicin was superior to the lower-dose regimen.<48>

At the American Society of Clinical Oncology annual meeting in May 1999, the results of 3 randomized trials evaluating high-dose chemotherapy plus stem-cell support were presented. The trials were conducted in the United States,<49> Scandinavia<50> and South Africa.<51> The

first 2 trials failed to demonstrate a benefit in favour of the high-dose chemotherapy. The South Africa trial demonstrated the superiority of the high-dose regimen. However, these results have recently been called into question because of scientific misconduct of the principal investigators.

In the CALGB trial 781 women with involvement of 10 or more nodes were randomly assigned to receive either high-dose CPB (cyclophosphamide, cisplatin and BCNU [bis-chloronitrosourea]) and bone marrow stem-cell support or intermediate-dose CPB.<49> No difference in either disease-free survival or overall survival was detected between the 2 groups (level I evidence). There was a 7.4% incidence of treatment-related deaths in the high-dose arm. These results were updated at the recent NIH Consensus Conference,<26> and there was still no difference in disease-free survival or overall survival between the groups.

In the Scandinavian Breast Cancer Study Group trial, 525 patients with high-risk primary breast cancer were randomly assigned to receive either 9 cycles of tailored FEC with granulocyte colony-stimulating factor or 3 cycles of FEC followed by high-dose chemotherapy with cyclophosphamide, thiotepa and carboplatin with stem-cell support.<50> Patients who received tailored FEC had a statistically significant improvement in disease-free survival. No difference in overall survival was detected between the groups (level I evidence).

In the trial by Bezwoda, 154 patients with primary breast cancer were randomly assigned to 2 cycles of high-dose CNVP (cyclophosphamide, mitoxatrone and etoposide) plus peripheral blood stem-cell transplant or 6 cycles of CAF.<51> At the median follow-up of 5 years, there was a statistically significant improvement in disease-free survival and overall survival in favour of the stem-cell transplant arm (level I evidence). [The validity of these results are in question because of scientific misconduct].

Two other trials presented at the 1998 American Society of Clinical Oncology meeting reported no benefit of high-dose chemotherapy plus stem-cell support versus standard chemotherapy in high-risk primary breast cancer.<52,53> These trials were of small sample size (level II evidence).

Adjuvant endocrine treatment

- **Ovarian ablation is effective in premenopausal women with 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 are ER-positive.**

Ovarian ablation (either by surgery or by radiotherapy) in premenopausal women with node-positive breast cancer has been used as adjuvant therapy for over 30 years. Its benefit has been demonstrated in the Early Breast Cancer Trialists' Collaborative Group Overview analysis (level I evidence).<11,54> Among 2100 women under 50 with early breast cancer (node positive and negative) who were randomly assigned to undergo ovarian ablation or not, there was a statistically significant improvement in survival at 15 years in favour of ovarian ablation (52.4% v. 46.1%).<54> The benefit appeared to be smaller in trials comparing ablation plus chemotherapy and chemotherapy alone. Also, the results suggested that ovarian ablation was not effective in women with ER-negative tumours.

In comparison with this evidence of the efficacy of ovarian ablation, the benefits of combination cytotoxic chemotherapy have been evaluated in larger numbers of patients and have been more amply demonstrated.<54> At present, chemotherapy remains the standard of care for premenopausal patients with positive nodes.

Apart from permanent castration with surgery or radiation, temporary ovarian ablation can be achieved with luteinizing hormone-releasing hormone (LHRH) agonists. LHRH agonists have theoretic appeal in that the endocrine intervention is finite and reversible, and the long-term morbidity of permanent ovarian dysfunction is avoided. Goserelin (Zoladex) has been shown to have a response rate similar to that of oophorectomy in premenopausal women with metastatic breast cancer.<55> Recently, preliminary results of trials evaluating Zoladex as adjuvant therapy have been reported. In the Eastern Cooperative Oncology Group trial, 1504 premenopausal women with node-positive, ER-positive cancer were randomly assigned to receive CAF alone,

CAF plus Zoladex for 5 years or CAF plus Zoladex and tamoxifen, both for 5 years.<56> The disease-free survival rates at 6 years were 67%, 70% and 78% respectively. The difference between CAF plus Zoladex and tamoxifen versus CAF alone was statistically significant.

In a Swedish trial, 2600 premenopausal women with early breast cancer were randomly assigned to receive tamoxifen, Zoladex, both or no endocrine treatment;<57> 43% of the women also received adjuvant chemotherapy. At a median follow-up of 4 years, the hazard ratio for women who received Zoladex was 0.77 (95% CI 0.66–0.90). No difference was detected in overall survival between the groups.

In a third trial conducted in Austria, 1045 premenopausal women with ER- or PR-positive tumours were randomly assigned to receive intravenous CMF for 6 cycles or Zoladex plus tamoxifen.<58> At a median follow-up of 4 years, the group who received Zoladex plus tamoxifen had a statistically significant improvement in recurrence-free survival.

In summary, although the results of trials evaluating Zoladex as adjuvant therapy are encouraging, they are preliminary, and it is unclear how this agent should be introduced into routine practice.

For patients who have ER-positive disease and who refuse chemotherapy, a hormonal intervention — either ovarian ablation or tamoxifen — should be offered. In a randomized trial, no significant difference between the outcomes of these interventions was found. However, the trial was not of sufficient size to establish their equivalence definitively (level II evidence).<59>

- **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.**

There is suggestive evidence that the addition of ovarian ablation to chemotherapy may confer added benefit. In the 1995 Overview analysis, at 15 years' follow-up of 550 women with ER-

positive tumours (mixed nodal status) who were less than 50 years of age at entry, ovarian ablation plus chemotherapy appeared to be more effective than chemotherapy alone in terms of recurrence-free survival and overall survival.<54> However, neither benefit was statistically significant.

The International Breast Cancer Study Group (Ludwig II) trial was included in the 1992 Overview analysis<11> and has since been published.<10> This study involved a 15-year follow-up of 327 premenopausal patients with 4 or more involved nodes. Overall, there was no difference in outcome between those who had oophorectomy before chemotherapy with CMF and prednisone (CMFP) and those treated with CMFP alone. However, in the subgroup of 107 patients with ER-positive tumours, those who had oophorectomy tended to have an improved disease-free survival compared with those given CMFP alone (23% [SD 5%] v. 15% [SD 5%], $p = 0.13$); the same was true for overall survival (41% [SD 7%] v. 30% [SD 7%], $p = 0.12$). This difference was despite the fact that 70% of the patients were rendered permanently amenorrheic from CMFP alone (level II evidence). The Southwest Oncology Group published the results of a trial comparing CMF, vincristine and prednisone (CMFVP) with oophorectomy followed by CMFVP in 314 premenopausal patients with node-positive disease. The 7-year survival rates were 71% in the oophorectomy and CMFVP group and 73% in the CMFVPonly group (level II evidence).<60>

These data suggest that larger studies may show a slightly improved disease-free survival when oophorectomy is added to chemotherapy. Confirmatory studies are being done with temporary medical castration, but no conclusions can yet be made.

- **Tamoxifen can be recommended in premenopausal women with ER-positive tumours who refuse chemotherapy or ovarian ablation.**

The Early Breast Cancer Trialists' Collaborative Group updated its Overview analysis of tamoxifen trials.<17> No benefit was observed among women with ER-negative tumours, and hence the results focused on women with ER-positive tumours. When the data were analyzed by

age and duration of tamoxifen therapy, the trials in which tamoxifen was given for 1 or 2 years demonstrated little benefit in both recurrence and mortality among women less than 50, whereas those in which tamoxifen was given for 5 years to women less than 50 revealed proportional risk reductions of 45% (SD 8%) in recurrence and 32% (SD 10%) in mortality.

It is important to examine whether tamoxifen alone has ever been shown to be superior or equivalent to chemotherapy in this population of premenopausal patients with node-positive cancer. Only 2 trials have prospectively compared chemotherapy alone with tamoxifen alone in premenopausal patients, and the results are contradictory. In the trial of the Italian Cooperative Group for Chemohormonal Therapy of Early Breast Cancer (GROCTA), 504 patients with node-positive, ER-positive disease were randomly assigned to 1 of 3 groups: tamoxifen for 5 years, 6 courses of intravenous CMF followed by 4 courses of epirubicin, or a combination of both regimens.<61> There were 237 patients in the premenopausal subgroup. In this subgroup, no significant differences were seen between the tamoxifen only patients and the chemotherapy only patients with respect to disease-free survival and overall survival, suggesting that tamoxifen is as effective as chemotherapy in premenopausal patients (level II evidence). However, patients taking tamoxifen alone had an excess of locoregional relapse in the first and third years after treatment, which the authors speculate may have been attributable to the possible hyperestrogenic effect of tamoxifen in premenopausal patients.

The results of the Gynecological Adjuvant Breast Group (GABG) study from Germany<62> contradict those of the GROCTA study. In that large, randomized, controlled trial, a subgroup of 331 patients less than 50 years old who were deemed “low risk” (1 to 3 positive nodes and steroid-receptor positive) were randomly assigned to receive intravenous CMF or tamoxifen for 2 years. Disease-free and overall survival rates were significantly improved in the CMF group. (Total relapse rates were 51.1% in the tamoxifen group compared with 15.7% in the CMF group, and total mortality was 20.4% in the tamoxifen group compared with 4.3% in the CMF group.) Confidence intervals were not given (level I evidence).

- **Whether tamoxifen should routinely be recommended after chemotherapy in premenopausal women is unclear.**

In the most recent Overview analysis, women who received 2 years of chemotherapy plus tamoxifen had a risk reduction of 22% (SD 4%) in recurrence and of 16% (SD 4%) in mortality compared with those who received chemotherapy alone.<16> The corresponding data for 5 years of chemotherapy plus tamoxifen versus chemotherapy alone were 52% (SD 8%) and 47% (SD 9%). Among women less than 50 years who received chemotherapy plus tamoxifen the risk reduction was 40% (SD 19%) in recurrence and 39% (SD 22%) in mortality compared with women who received only chemotherapy. However, the data for this subgroup are not reliable because of the relatively small number of patients (level II evidence). Hence, although the results suggest that the addition of tamoxifen to chemotherapy may improve disease-free survival and overall survival compared with chemotherapy alone, the results are in no way conclusive. The National Cancer Institute of Canada Clinical Trials Group is addressing this issue. Recruitment is complete for a trial in which premenopausal women with node-positive breast cancer who have completed adjuvant chemotherapy have been randomly assigned to receive either tamoxifen or placebo.

- **Before recommending hormonal therapy in premenopausal women, both the long-term side effects and its effects on recurrence must be considered.**

The long-term adverse consequences of menopause include osteoporosis and an increase in cardiovascular deaths.<63> However, the Overview analysis did not demonstrate any excess non-breast-cancer-related mortality in the oophorectomy subgroup.<11> In the most recent Overview analysis, the proportional reduction in the risk of contralateral breast cancer was 26% (SD 9%) for 2 years of tamoxifen and 47% (SD 9%) for 5 years of tamoxifen.<17> The proportional risk reduction was independent of age. This suggests that 5 years of tamoxifen approximately halves the annual incidence rate of contralateral breast cancer. In absolute terms, the 10-year risk is reduced from approximately 47 per 1000 to 26 per 1000 with 5 years of

tamoxifen. In contrast, 5 years of tamoxifen was associated with an approximately 4-fold increase in the rate of endometrial cancer. This corresponds to a 10-year risk of 11 per 1000 with tamoxifen and 3 per 1000 in the control group. There was a statistically significant increase in an annual excess mortality related to endometrial cancer of 0.2 per 1000. The non-breast-cancer-related mortality did not differ for other causes of death, including vascular causes. Use of tamoxifen has been reported to be associated with an increased risk of cataract (posterior subcapsular opacities) in the NSABP B-14 trial and an increased likelihood of undergoing cataract surgery in the Breast Cancer Prevention Trial.<64> In addition, this trial provided reliable estimates of the rates of thromboembolism and endometrial cancer among women who received tamoxifen compared with those who received a placebo.<64>

Finally, in a recent randomized controlled trial, the use of tamoxifen prevented bone mineral loss in the spine and was associated with significantly decreased indices of bone turnover in postmenopausal patients with breast cancer (level I evidence).<65>

Postmenopausal women

Adjuvant endocrine treatment

- **Postmenopausal women with stage II, ER-positive cancer should be offered adjuvant tamoxifen.**

Tamoxifen, when used as systemic adjuvant therapy in postmenopausal women with stage II breast cancer, decreases the risk of recurrence and mortality (level I evidence). The benefit occurs in women with ER-positive disease.<17>

Tamoxifen is the only form of adjuvant systemic therapy that has been adequately evaluated in women over 70 years of age. Many randomized controlled clinical trials have been conducted to assess the role of adjuvant tamoxifen in the treatment of breast cancer. In the Overview analysis, 5 years of tamoxifen was associated with a risk reduction of 43% (SD 5%) in recurrence and

28% (SD 6%) in mortality among women with node-positive, ER-positive cancer.<17> This corresponds to an absolute reduction of 15.2% in recurrence and 10.9% in mortality at 10 years. The Overview analysis also included results by age for 5 years of tamoxifen treatment in patients with ER-positive cancer (node-positive and node-negative combined). The risk reduction in recurrence for the age groups 50–59, 60–69 and ≥ 70 years were 37% (SD 6%), 54% (SD 5%) and 54% (SD 15%) respectively. The corresponding data for mortality were 11% (SD 8%), 33% (SD 6%) and 34% (SD 13%).

- **The recommended duration of tamoxifen therapy is 5 years.**

There is level I evidence that tamoxifen when given for 2 years is less effective than when given for 5 years.<66> This finding is also supported by indirect comparisons in the Overview analysis.<17> There is also level I evidence that a 10-year course of tamoxifen is no more effective than a 5-year course of this therapy.<67,68> Since the level of toxicity is relatively low, most centres continue tamoxifen for 5 years (level IV evidence) (see also guideline 7).

- **No other hormonal intervention apart from tamoxifen can be recommended for postmenopausal patients.**

An ongoing trial in Scandinavia is exploring the use of alternating tamoxifen and medroxyprogesterone acetate compared with tamoxifen alone in postmenopausal patients.

Another study investigated the use of adjuvant aminoglutethimide therapy in postmenopausal patients.<69> In this study, 354 women with node-positive disease were randomly assigned to receive either aminoglutethimide (250 mg 4 times daily, orally) for 2 years or placebo. No survival benefit was seen in the treatment group (level II evidence). Finally, the Arimidex Tamoxifen Alone or Combined (ATAC) trial is comparing the aromatase inhibitor Arimidex (anastrazole) alone, tamoxifen alone and a combination of the 2 drugs in postmenopausal women with early breast cancer.

Adjuvant chemotherapy

- **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.**

Many clinical trials have assessed the role of adjuvant chemotherapy in women with node-positive breast cancer (level I evidence). In the early trial of Bonadonna and associates,<34> 386 women between 26 and 75 years of age (including 201 postmenopausal women) were randomly assigned after mastectomy to receive either CMF for 12 cycles or no further therapy. Among the postmenopausal patients, after 20 years of follow-up there was no significant difference in disease-free or overall survival between the adjuvant CMF group and the control group (level II evidence). Bonadonna and Valagussa<47> felt the difference between premenopausal and postmenopausal patients was due to "the low dose of chemotherapy that many postmenopausal patients received."

In the most recent Overview analysis, the risk reduction in recurrence for women given chemotherapy was 22% (SD 4%) among those aged 50–59 and 18% (SD 4%) among those aged 60–69.<16> (This finding was for node-positive and node-negative disease combined.) The corresponding data for mortality were 14% (SD 4%) and 8% (SD 4%). There were too few patients over 70 years enrolled in the trials for there to be information on the effect of chemotherapy in this age group. The absolute difference in recurrence at 10 years in the group of women 50–69 years with node-positive disease was 5.4%; the corresponding difference in mortality was 2.3%.

Thus, the meta-analysis demonstrated a modest benefit with chemotherapy in postmenopausal women. However, because the benefit is small, it must be weighed against the side effects and risks and discussed with the patient.

In the Intergroup trial involving postmenopausal women, there was a statistically significant

improvement in disease-free survival with AC followed by paclitaxel compared with AC alone, particularly in patients with ER-negative tumours.<25,26> The NSABP B-28 trial did not detect a difference between these 2 regimens in postmenopausal women.<26> The National Cancer Institute of Canada Clinical Trials Group MA5 trial, which demonstrated improved disease-free survival and overall survival in favour of CEF over CMF, included women up to 55 years.<22> The potential incremental benefit of the addition of paclitaxel to AC over AC alone and CEF over CMF must be weighed against the increase in side effects.

Adjuvant chemotherapy is given less frequently to women older than 70 years than to younger women.

Chemotherapy plus tamoxifen

- **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.**

In the NSABP B-16 trial, women over the age of 50 years with node-positive tumours were randomly assigned to receive either tamoxifen (389 patients) or AC plus tamoxifen (385 patients) for 5 years.<70> At 7 years' follow-up there was a statistically significant improvement in outcome in favour of the combined therapy: disease-free survival was 62% among those taking the combined therapy compared with 49% among those taking tamoxifen alone, and overall survival was 74% and 65% respectively.

The Ludwig group study (Ludwig III) evaluated 463 postmenopausal patients with node-positive breast cancer aged 65 years and under after mastectomy and axillary clearance (33% had ER-positive tumours, 18% had ER-negative tumours, and in 49% the ER status was unknown).<71> Patients were randomly assigned to 3 groups: CMF for 12 cycles plus prednisone plus tamoxifen for 1 year (CMFpT), prednisone and tamoxifen (pT) or no adjuvant therapy. At a median follow-up of 9 years the disease-free survival was 41% in the CMFpT group, 31% in the pT group and 19% in the control group ($p < 0.0001$).<72> The overall survival was 53% in the CMFpT group,

41% in the pT group and 38% in the control group ($p = 0.08$) (level I evidence).

The National Cancer Institute of Canada Clinical Trials Group conducted a trial in which 706 postmenopausal patients with node-positive and ER- or PR-positive breast cancer received either tamoxifen for 2 years or tamoxifen for 2 years plus CMF for 8 cycles, given concurrently.<73> There was no difference in disease-free or overall survival between the 2 groups (level II evidence). Side effects, including infection, nausea and vomiting, mucositis, diarrhea, leukopenia, thrombocytopenia and thromboembolism, were each significantly more common in the group taking CMF plus tamoxifen than in the group given tamoxifen alone (level I evidence).

Three recent trials have compared tamoxifen with tamoxifen plus chemotherapy. In the Intergroup trial, postmenopausal women with node-positive, ER-positive tumours were randomly assigned to receive tamoxifen alone, CAF followed by tamoxifen or CAF plus tamoxifen. There was a statistically significant improvement in the 4-year disease-free survival in favour of CAF plus tamoxifen (79%) compared with tamoxifen alone (72%). There was no difference in overall survival between the groups.<74>

In the International Breast Cancer Study Group trial, postmenopausal women with node-positive, ER-positive tumours were randomly assigned using a factorial design to receive tamoxifen alone, tamoxifen plus early CMF, tamoxifen plus delayed CMF or tamoxifen plus early and delayed CMF.<75> The addition of chemotherapy to tamoxifen was associated with a significant (24%) reduction in recurrence compared with tamoxifen alone. There was no significant difference in overall survival between the groups (level I evidence).

In a European trial, postmenopausal women were randomly assigned to receive tamoxifen for 4 years or epirubicin plus tamoxifen. There was a statistically significant improvement in recurrence-free survival with the addition of epirubicin to tamoxifen.<76> No difference was detected in overall survival between the groups.

In the Overview analysis involving women aged 50–69, there was a proportional reduction in

recurrence of 19% (SD 3%) with chemotherapy plus tamoxifen compared with tamoxifen alone.<16> The corresponding proportional reduction in mortality was 11% (SD 4%).

All ages

- **The routine use of bisphosphonates as adjuvant therapy cannot yet be recommended.**

Three trials have evaluated the use of bisphosphonates to prevent breast cancer metastases. In a German study involving 302 patients with primary breast cancer that had spread to the bone marrow, oral clodronate therapy for 2 years significantly reduced the number of bone and visceral metastases.<77> In a trial involving over 1000 women with primary operable breast cancer, oral clodronate therapy for 2 years reduced the risk of bone metastases compared with placebo ($p = 0.054$).<78> In contrast, a third study showed a detrimental effect of 3 years of clodronate therapy in both recurrence-free and overall survival.<79>

Clinical trials

- **Patients should be offered the opportunity to participate in clinical trials whenever possible.**

Improvement in the care of future patients with breast cancer is dependent on the participation of sufficient numbers of patients in clinical trials. Physicians treating patients with breast cancer should therefore be aware of currently available trials and should give patients the chance to participate.

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