Correspondance

Treatment of locally advanced breast cancer

As the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer points out,¹ locally advanced breast cancer comprises a heterogeneous group of breast tumours. Because of the complex needs of these patients, including the requirement for combined-modality treatment, we have established a specialized clinic for the treatment of women with locally advanced breast cancer at the Toronto–Sunnybrook Regional Cancer Centre, the first and largest of its kind to provide appropriate interdisciplinary care² for this group of patients.

We would like to add a few points to the analysis presented by the Steering Committee. The recently published guideline¹ discusses only the role of chemotherapy in the neoadjuvant setting. Currently, however, neoadjuvant hormonal therapy with third-generation aromatase inhibitors is gaining importance in this population, especially for an elderly, postmenopausal woman whose breast cancer is positive for estrogen receptor or progesterone receptor. The importance of neoadjuvant therapy with aromatase inhibitors and the superiority of these agents over tamoxifen in this setting has been demonstrated in 2 randomized trials.^{3,4}

The authors discuss the evolving role of aromatase inhibitors in the adjuvant setting,⁵ but other recent studies have shown the benefit of these drugs after tamoxifen.^{6,7} The rapidly accumulating evidence in favour of aromatase inhibitors necessitates frequent updating of guidelines with respect to adjuvant hormonal therapy.

Taxane therapy should now be considered the standard of care. The authors mention the results of 2 large trials^{8,9} that clearly showed a substantial improvement in the pathologic response among patients receiving taxanes in addition to anthracyclines. Recent presen-

tation of longer follow-up to one of these studies¹⁰ provides more evidence of improvement in survival with the addition of taxane chemotherapy.

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We would like to raise another issue related to adjuvant chemotherapy for the treatment of women with locally advanced breast cancer.¹ For adjuvant therapy of patients with node-positive, operable breast cancer, cross-trial comparison over similar follow-up periods has indicated a greater risk of acute leukemia with more anthracyclines and alkylators. Specifically, among patients treated with 4 cycles of adriamycin and cyclophosphamide (AC) followed by 4 cycles of paclitaxel, the incidence of acute leukemia ranged from 0.25% over a 69-month follow-up period² to 0.18% over a 36-month follow-up period.³ For regimes of 6 cycles of anthracyclines and alkylating agents, the risk of acute leukemia was much greater: 1.42% over 59 months with cyclophosphamide, epirubicin and fluorouracil (CEF)⁴ and 1.17% over 48 months with epirubicin and cyclophosphamide.⁵ Even as therapy with AC followed by paclitaxel is being compared with a CEF regimen in the randomized phase III MA.21 trial (being conducted by the Clinical Trials Group of the National Cancer Institute of Canada), this side effect profile should not be ignored in discussions of adjuvant chemotherapy.

Given these data, the use of taxanes should be covered in clinical guideline development.

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In their guidelines for managing locally advanced breast cancer, Tamara Shenkier and associates¹ mention the difficulty they faced in dealing with changes that were made to the tumour-node-metastasis (TNM) tumour-staging system in 2002 (Table 1). Their comment on this point needs amplification because, if anything, it understates the potential confusion caused by the introduction of a new category, stage IIIC.

Stage IIIC is defined as applying to patients with any T category and pN3 disease (Table 2). pN3 disease in turn has 3 subcategories, the third of which (pN3c), supraclavicular node involvement, is the focus of the comments by Shenkier and associates.¹ As they state, there is now some evidence to support treating these patients as having inoperable locally advanced, rather than metastatic, disease. However, pN3a and pN3b represent types of nodal involvement (more than 10 axillary, infraclavicular and internal mammary nodes) that have little or nothing to do with operability. Most such patients would be managed in the manner that

Shenkier and associates describe for operable stage IIIA disease.

It is unfortunate that the newly introduced stage IIIC category includes 2 groups of patients for whom management strategies are quite different. Indeed, its utility as a descriptive category must be questioned, particularly in the context of management guidelines. In

this setting it might have been better to use specific T and N categories, since the guideline as published appears to imply that stage IIIC is equivalent to supraclavicular node involvement.

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Table 1: TNM staging system for breast cancer²

Stage	Tumour status*	Node status†	Metastasis status‡
0	Tis	N ₀	M ₀
I	T ₁	N ₀	M ₀
IIA	T ₀ T ₁	N ₁ N ₁	M ₀ M ₀
IIB	T ₂ T ₂ T ₃	N ₀ N ₁ N ₀	M ₀ M ₀ M ₀
IIIA	T ₀ T ₁ T ₂ T ₃ T ₃	N ₂ N ₂ N ₂ N ₁ N ₂	M ₀ M ₀ M ₀ M ₀ M ₀
IIIB	T ₄ T ₄ T ₄	N ₀ N ₁ N ₁	M ₀ M ₀ M ₀
IIIC	Any T	N ₃	M ₀
IV	Any T	Any N	M ₁

*Tumour status: Tis = carcinoma in situ; T₀ = no evidence of primary tumour; T₁ = tumour ≤ 2 cm in greatest dimension; T₂ = tumour > 2 cm but not > 5 cm in greatest dimension; T₃ = tumour > 5 cm in greatest dimension; T₄ = tumour of any size with chest-wall extension, ulceration, peau d'orange or inflammatory breast cancer.

†Node status: N₀ = no regional lymph-node metastasis; N₁ = metastasis in movable ipsilateral axillary lymph node(s); N₂ = metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph-node metastasis; N₃ = metastasis in ipsilateral internal mammary lymph node(s) or in ipsilateral supraclavicular lymph node(s).

‡Metastasis status: M₀ = no distant metastasis; M₁ = distant metastasis.

Table 2: Definitions of pN3 breast cancer and its subcategories

Category	Definition ³
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph node(s) in the presence of 1 or more positive axillary lymph node(s); or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumour deposit > 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph node(s); or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes