EDITORIAL

Counterpoint

Tamoxifen and Breast Conservation

Do We Still Need Radiotherapy?

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After more than two decades of increasingly widespread use, the benefits of the antiestrogen tamoxifen in the adjuvant treatment of operable breast carcinoma are universally recognized. The very significant reductions in breast carcinoma recurrences and disease specific deaths associated with tamoxifen administration have been documented extensively by meta-analyses,[1] and favorable effects on contralateral breast carcinoma incidence, cardiovascular deaths, and skeletal mineral density also have been attributed to this generally well tolerated drug.[2] However, few authors have drawn attention to the particular efficacy of tamoxifen in reducing locoregional failure rates and the intriguing implications of this finding for patients undergoing breast-conserving therapy.

In fact a marked reduction of initial failures in local and regional sites has been a striking feature of the early adjuvant trials of single agent tamoxifen.[3,4] However, because the large majority of patients had undergone total mastectomy, no conclusions could be drawn from these studies regarding the potential role of tamoxifen in improving the possibilities of breast preservation. Based on early results from the B-14 Trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP), Fisher et al. were the first to publish prospective data suggesting that ipsilateral breast tumor recurrence (IBTR) might be reduced significantly by tamoxifen.[5] Results from a substratum of the Stockholm Tamoxifen Trial presented in this issue of *Cancer* by Dalberg et al.,[6] taken along with a recent update of the B-14 Trial,[7] now provide powerful evidence that tamoxifen added to radiotherapy does reduce IBTR by at least a factor of two compared with radiotherapy alone. The resultant 10-year IBTR rates (3% for both Dalberg et al. and Fisher et al.) are among the lowest ever reported, indicating a degree of local control at least as effective as that achieved by total mastectomy.[5,6]

However, the article by Dalberg et al. raises a certain number of questions that merit additional commentary. First, which patients stand to benefit from the protective effect of tamoxifen regarding IBTR? Although the Stockholm study addressed exclusively low risk, lymph node negative, postmenopausal, predominantly estrogen receptor (ER) positive patients, it is clear from NSABP B-14 that ER positive premenopausal patients benefit to a similar degree.[7] Nor is there reason to believe that a similar benefit should not be expected in ER positive patients with a higher potential tumor burden, such as

See referenced original article on pages 2204–11, this issue.

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Received February 26, 1998; accepted March 5, 1998.

those with positive axillary lymph nodes (ALN), larger tumors, or nonnegative resection margins. There are insufficient data regarding patients with ER negative tumors, who often are assumed, perhaps without sufficient justification, not to benefit significantly from tamoxifen.

Second, is the high local control observed after radiotherapy and tamoxifen simply a reflection, as one might assume, of an independent and additive effect of the two agents? In both the B-14 and Stockholm Trials radiotherapy was administered to patients already receiving tamoxifen, and an interaction thus can not be excluded. Although such potential interactions have not been studied extensively, tamoxifen appears if anything to reduce the radiosensitivity of ER positive breast carcinoma cells,[8,9] and it is perhaps remarkable that such excellent clinical results could be obtained from their simultaneous administration. Moreover, the stimulation by tamoxifen of certain cytokines, such as transforming growth factor-β, might give rise to other unfavorable interactions, such as the induction of radiation fibrosis.[10] However, retrospective studies do not suggest any striking effect of tamoxifen administration on the cosmetic aspects in the conserved breast.[11,12]

The most provocative question raised by Dalberg et al. concerns the possibility that the protection afforded by tamoxifen might allow at least selected patients to be treated safely by breast-conserving surgery without radiotherapy. However, it should be remembered that the apparent ''protective'' effect of tamoxifen demonstrated by both Dalberg et al. and Fisher et al. was observed in patients receiving radiotherapy.[5,6] It thus is not entirely clear whether the same effect is operative in the absence of breast irradiation, although this is quite likely. Nevertheless, the few data on IBTR in conservatively operated but unirradiated patients receiving tamoxifen are not encouraging. In the Scottish Conservation Trial a 25% IBTR rate was observed without breast irradiation in ER positive, conservatively operated patients receiving tamoxifen, despite the fact that the subpopulation of patients at highest risk for recurrence, namely premenopausal patients with positive ALN, had not been included in the study.[13]

Breast irradiation has a powerful effect on IBTR, reducing its incidence by a factor of between four and six compared with conservation surgery alone.[5,13–15] Based on prognostic factors such as age, morphology, and resection margin width it may be possible in the future to identify patients who do not require the high degree of protection provided by radiotherapy. However, thus far it has been difficult to define reliably low risk subgroups with 10-year IBTR rates much lower than 20% after lumpectomy alone.[15,16] In older patients satisfactory local control may be possible in favorable small tumors, widely excised by sector resection[14] or quadrantectomy.[17] However, it is less likely that satisfactory results could be obtained without radiotherapy, even in such a favorable setting, using cosmetically more acceptable lumpectomy. Although the use of tamoxifen is likely to improve the results of breast-conserving surgery alone, more solid data are required before elimination of breast irradiation can be accepted as a safe option. These issues currently are under investigation in ongoing or recently completed clinical trials.

Finally, Dalberg et al. appropriately call attention to the cost and inconvenience of breast irradiation as well as to the need to inform patients regarding the potential advantages and risks of tamoxifen administration. Indeed, in many countries the role played by the medical care consumer in the decision-making process is becoming increasingly important. Patients will certainly welcome the two to three-factor protection against IBTR provided by tamoxifen, especially in the light of the overall reduction in breast carcinoma-related events associated with this agent. However, it is questionable whether the well informed patient will choose to forgo the four to six-factor protection afforded by breast irradiation, even in the face of low absolute risk. In fact, recent studies suggest that patients strongly tend to prefer undergoing breast irradiation, even when the potential clinical benefit is perceived as small.[18,19]

Increasing the chances of breast conservation clearly can now be counted among the clinical benefits of tamoxifen. Although this effect has been documented convincingly in patients receiving tamoxifen and radiotherapy concomitantly, it is likely that the benefit is to a great extent independent of any interaction with radiation. Little is known regarding the importance of sequencing, dosage, or duration of tamoxifen administration in this setting, but a significant local control benefit can be expected with schedules currently in use. Whether tamoxifen will allow certain low risk patients to be treated without radiotherapy is a question worthy of future investigation. In the interim, breast irradiation should continue to be considered the standard of care after breast conservation surgery for patients with invasive breast carcinoma.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 1992;339:1–15.

2. Jaiyesimi IA, Buzdar AU, Decker DA, Hortobagyi GN. Use of tamoxifen for breast cancer: twenty-eight years later. *J Clin Oncol* 1995;13:513–29.
3. Stewart HJ for the Scottish Cancer Trials Breast Group. The Scottish trial of adjuvant tamoxifen in node-negative breast cancer. *Monogr Natl Cancer Inst* 1992;11:117–20.
4. ''Nolvadex'' Adjuvant Trial Organisation. Controlled trial of tamoxifen as a single agent in the management of early breast cancer. *Br J Cancer* 1988;57:608–11.
5. Fisher B, Costantino J, Redmond C, Poisson R, Bowman D, Couture J, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med* 1989;320:479–84.
6. Dalberg K, Johansson H, Johansson U, Rutqvist LE. A randomized trial of long term adjuvant tamoxifen plus postoperative radiation therapy versus radiation therapy alone for patients with early stage breast carcinoma treated with breast-conserving surgery. *Cancer* 1998;82: 2204–11.
7. Fisher M, Dignam J, Bryant J, DeCillis A, Wickerham DL, Wolmark N, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst* 1966;88:1529–42.
8. Paulsen GH, Strickert T, Marthinsen AB, Lundgren S. Changes in radiation sensitivity and steroid receptor content induced by hormonal agents and ionizing radiation. *Acta Oncol* 1996;35:1101–9.
9. Wazer DE, Joyce M, Chan W, Gewirtz D, Lin P-S, Solares G, et al. Effects of tamoxifen on the radiosensitivity of hormonally responsive and unresponsive breast carcinoma cells. *Radiat Oncol Invest* 1993;1:20–8.
10. Bentzen SM, Skoczylas JZ, Overgaard M, Overgaard J. Radiotherapy-related lung fibrosis enhanced by tamoxifen. *J Natl Cancer Inst* 1996;88:918–22.
11. Wazer DE, Morr J, Erban JK, Schmid CH, Ruthazer R, Schmidt-Ullrich RK. The effects of postradiation treatment with tamoxifen on local control and cosmetic outcome in the conservatively treated breast. *Cancer* 1997; 80:732–40.
12. Fowble B, Fein DA, Hanlon AL, Eisenberg BL, Hoffman JP, Sigurdson ER, et al. The impact of tamoxifen on breast recurrence, cosmesis, complications, and survival in estrogen receptor-positive early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 1996;35:669–77.
13. Forrest AP, Stewart HJ, Everington D, Prescott RJ, McArdle CS, Harnett AN, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet* 1996;348:708–13.
14. Liljegren G, Lindgren A, Bergh J, Nordgren H, Tabar L, Holmberg L. Risk factors for local recurrence after conservative treatment in stage I breast cancer. Definition of a subgroup not requiring radiotherapy. *Ann Oncol* 1997;8: 235–41.
15. Clark RM, Whelen T, Levine M, Roberts R, Wlllan A, McCulloch P, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst* 1996;88: 1659–64.
16. Schnitt SJ, Hayman J, Gelman R, Eberlein TJ, Love SM, Mayzel K, et al. A prospective study of conservative surgery alone in the treatment of selected patients with stage I breast cancer. *Cancer* 1996;77:1094–100.
17. Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med* 1993;328:1587–91.
18. Palda VA, Llewellyn-Thomas HA, Mackenzie RG, Pritchard KI, Naylor CD. Breast cancer patients' attitudes about rationing postlumpectomy radiation therapy: applicability of trade-off methods to policy making. *J Clin Oncol* 1997;15: 3192–200.
19. Hayman JA, Fairclough DL, Harris JR, Weeks JC. Patient preferences concerning the trade-off between the risks and benefits of routine radiation therapy after conservative surgery for early-stage breast cancer. *J Clin Oncol* 1997; 15:1252–60.