Rationale for extended adjuvant letrozole after five years of tamoxifen in postmenopausal oestrogen receptor–positive women with early-stage breast cancer

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1. INTRODUCTION

Hormonal therapy has been an integral component of the adjuvant strategy for women with hormone receptor–positive breast cancer for decades. Although the role for tamoxifen is well established, the recent emergence of data in support of aromatase inhibitors (AIs) in postmenopausal women is changing adjuvant management. Multiple randomised controlled trials have confirmed a role for adjuvant AIs, but the optimal approach remains unclear. Questions regarding timing and duration of therapy persist, as do questions regarding risks and side effects. The American Society of Clinical Oncology (ASCO) panel on technology recently concluded that AIs should be incorporated into the adjuvant strategy for postmenopausal women, but no single therapeutic strategy was advocated over any other [1]. Here, we review the rationale for extended adjuvant letrozole therapy after 5 years of tamoxifen for postmenopausal women with oestrogen receptor–positive (ER+) early breast cancer.

2. TAMOXIFEN VERSUS AROMATASE INHIBITORS: MECHANISMS OF ACTION AND SIDE EFFECTS

Tamoxifen is a selective oestrogen receptor modulator with both agonist and antagonist properties. The antagonistic mechanism confers the demonstrated breast cancer benefits, which include a reduction in the risk of breast cancer death by 31% with 5 years of daily tamoxifen therapy, regardless of age or use of chemotherapy [2]. The agonist properties of tamoxifen provide protection against osteoporosis in postmenopausal women, but they also promote endometrial hyperplasia, an effect that appears to be time- and dose-dependent. Studies have demonstrated that the relative risk of endometrial cancer is from double to quadruple that of an age-matched population. However, the endometrial tumours tend to be low-grade, early-stage, and surgically curable. Other side effects related to the oestrogenic properties of tamoxifen include an increased incidence of thromboembolic events. Tamoxifen has also been associated with an improved lipid profile, although the clinical implications of that finding have not yet been elucidated [3].

Letrozole, anastrozole, and exemestane belong to the family of third-generation AIs. Letrozole and anastrozole are nonsteroidal compounds that reversibly inhibit aromatase, the enzyme responsible for conversion of peripheral androgens to oestrogens, and thus, for oestrogen synthesis in postmenopausal women [4]. In the metastatic setting, letrozole has proven more effective than anastrozole in reducing circulating oestrogen levels; however, the clinical relevance of that finding remains uncertain [5]. Exemestane is a steroidal, irreversible inhibitor of the aromatase enzyme and similarly reduces circulating levels of oestrogens [4]. Whether the variations in AI structure confer any clinically significant difference in terms of side effect or long-term toxicity profiles has yet to be established. To date, no head-to-head comparisons of the various AIs have been reported.

The AIs are not associated with a significantly increased risk of thromboembolic disease or endometrial hyperplasia, but they are associated with an increased risk of osteoporosis and fractures. In the National Cancer Institute of Canada (NCIC) MA-17 trial, the incidence of fractures with letrozole was 3.6% as compared with 2.9% in the placebo group ($p = 0.24$). The risk of serious cardiovascular events has also been closely monitored. In MA-17, no significant difference was found between observed cardiovascular events in patients taking letrozole [175 (6.8%)] and in those taking placebo [167 (6.5%)] [6]. AIs are also associated with hot flashes, vaginal dryness, myalgias and arthralgias.

3. OPTIMAL DURATION OF TAMOXIFEN THERAPY

As outlined in the 2000 Oxford Review, 5 years of tamoxifen showed a trend for greater benefit conferred than did a duration of 1 or 2 years [2]. In the National Surgical Adjuvant Breast and Bowel Project B-14 study, patients derived a significant benefit from 5 years of tamoxifen therapy, but had a worse disease-free survival (DFS) and overall survival (OS) with

10 years of tamoxifen [7] Thus, for patients treated with tamoxifen, 5 years of therapy appears to be the ideal.

4. THE EVIDENCE FOR ADJUVANT AROMATASE INHIBITORS

Several large randomised trials have investigated the role of third-generation AIs in the adjuvant setting. The Arimidex, Tamoxifen Alone or in Combination trial investigated the roles of anastrozole or tamoxifen alone or as a combination as the initial adjuvant hormonal manoeuvre. After a median follow-up of 68 months, patients treated with anastrozole had a 17% improved DFS as compared with tamoxifen [8,9]. In the Intergroup Exemestane Study, women were randomised to tamoxifen or exemestane after 2 – 3 years of tamoxifen for a total duration of therapy of 5 years [10]. Women who were switched to exemestane had a 32% reduction in DFS as compared with those who continued tamoxifen. Similarly, results of the BIG 1-98 trial were recently presented at both the ASCO and St. Gallen 2005 meetings, and the most recent data from that study showed, in the letrozole arm, a 19% improvement in DFS at 26 months as compared with tamoxifen.

In the NCIC MA-17 study, women were randomised to either placebo or letrozole upon completion of 5 years of adjuvant tamoxifen. That study was unblinded after only 2.4 years of follow-up because of the interval detection of a 40% reduction in DFS among women treated with letrozole, conferring an absolute benefit of 6%. In patients with node-positive breast cancer, a 39% reduction in risk of death was also seen, making this adjuvant AI trial the first to demonstrate a survival benefit [6,11]. An extension of MA-17 is underway, with women previously randomised to the letrozole arm being offered further randomisation to an additional 5 years of letrozole or placebo.

5. THE NATURAL HISTORY OF BREAST CANCER

A number of studies have described the natural history of breast cancer, an appreciation of which is essential for establishing effective treatment decisions. Saphner *et al.* investigated the outcome of patients enrolled in seven completed, unblinded clinical trials of adjuvant therapy conducted by the Eastern Cooperative Oncology Group [12]. Increased nodal involvement conferred a higher risk of both early and late relapses (defined, respectively, as within 0 – 5 years and beyond 5 years). Overall, risk of recurrence peaked during years 1 – 2, with a tapering of risk thereafter. In a subgroup analysis of ER+ and ER– women, recurrence risk decreased among the ER– cohort between years 5 and 8 and years 8 and 12, but remained relatively stable among the ER+ cohort during the same periods.

To better elucidate the natural history of early-stage breast cancer, Chia *et al.* reviewed 10-year outcomes among a cohort of node-negative and lymphatic invasion–negative patients treated with local therapy alone [13]. The investigators demonstrated that tumour size and grade were powerful prognosticators of relapse and mortality within the 10-year period. With the exception of grade 1 T1 tumours, the risk of relapse was sustained throughout the 5- to 10-year period. Thus, tumour size and grade are important prognosticators of both early and late relapse among patients with early-stage, node-negative breast cancer.

To define breast cancer risk among postmenopausal women who have received tamoxifen for 5 years, Kennecke *et al.* surveyed the British Columbia Cancer Agency Breast Cancer Outcomes Database [14]. Ten-year outcome was determined for 1086 women aged 45 years or older who were living in British Columbia at the time of diagnosis and who were treated with adequate local therapy plus or minus chemotherapy. Endpoints were event-free survival (EFS—defined as locoregional or distant recurrence, second primary breast cancer, or breast cancer–related death) and breast cancer–specific survival (BCSS). Of the variables examined, nodal status and, to a lesser degree, increasing tumour size and grade proved to be significant predictors of both EFS and BCSS 10 years after diagnosis (Table I).

Table II shows outcomes of node-negative patients according to grade. Low-grade node-negative breast cancer was associated with a very low breast cancer event rate and no breast cancer deaths during the second 5 years after tamoxifen [14]. Grade 2 or 3 histology was associated with a significantly increased risk of breast cancer events and breast cancer–specific mortality. These findings highlight the importance of grade in the risk stratification of node-negative patients; they are also consistent with previous findings described in the literature [13].

The prognostic impact of T and N stage alike is further illustrated by the statistically significant pairwise comparisons depicted in Kaplan–Meier EFS curves (Figure 1).

6. PATIENT SELECTION FOR EXTENDED ADJUVANT THERAPY WITH LETROZOLE

The benefits of extended adjuvant letrozole after 5 years of tamoxifen as described in MA-17 mean that physicians are now faced with treatment decisions that require an estimation of the breast cancer risk and the benefits of therapy.

To identify appropriate candidates for extended adjuvant letrozole, patients may be stratified into low- (<5%), moderate- (5% – 15%), and high-risk (>15%) categories based on event rate estimates as outlined in Table III. In low-risk patients (such as those with low-grade T1 N0 tumours), extended adjuvant

TABLE I Multivariate analysis of relative risk (RR) for selected patient and tumour characteristics 10 years after diagnosis among postmenopausal oestrogen receptor–positive women treated with 5 years of tamoxifen [14]

	Frequency (%)	*Breast cancer–specific survival RR*	*Event-free survival [a] RR*
Tumour size (cm)			
0.1–1.0	14.7	0.559	0.878
1.1–2.0	41.5	1	1
2.1–5.0	39.9	2.566	1.568
Grade			
1	9.9	0.662	0.303
2	52.7	1	1
3	28.2	0.971	1.250
Positive nodes (*n*)			
0	42.4	1	1
1–3	38.0	3.157	1.739
4–9	11.5	5.875	3.039

[a] Defined as absence of locoregional or distant recurrence, new contralateral breast cancer, or breast cancer–related death. The reference group is assigned a value of 1.

TABLE II Breast cancer–specific event rates and mortality among postmenopausal oestrogen receptor–positive women 5 years after completing tamoxifen [14]

TNM stage [a]	*Event rate, years 6–10 (%)*	*Mortality, years 6–10 (%)*
T1 N0		
Grade 1	3.6	0
Grade 2	11.4	1.5
Grade 3	11.5	5.2
T2 N0		
Grade 1	0	0
Grade 2	10.2	8.5
Grade 3	13.0	5.4
N1 (1–3 nodes positive)	15.9	9.9
N2 (4–9 nodes positive)	32.1	21.7

[a] TNM = tumour, node, metastasis; T1 = <2-cm tumour; T2 = 2- to 5-cm tumour; N0 = 0 nodes positive; N1 = 1 – 3 nodes positive; N2 = 4 – 9 nodes positive [15].

therapy is likely of limited benefit because of the low risk of recurrence. In high-risk patients (such as those with node-positive disease), extended therapy should be considered in the absence of contraindications, significant comorbidities, or limited 5-year life expectancy. In node-positive patients, the estimated 40% improvement in EFS and the 39% improvement in OS associated with letrozole therapy as outlined in the MA-17 study will often outweigh the potential treatment-related toxicities and risks for most patients.

Women at moderate risk for recurrence may include those with node-negative grade 2 or 3 tumours. The risks of therapy and the 5-year survival should be considered. To illustrate a risk–benefit calculation, a woman with a breast cancer event risk of 10% during the second 5 years after tamoxifen could be expected to obtain an absolute EFS benefit of 4% from extended adjuvant letrozole. For most healthy postmenopausal women, that level of benefit could be expected to exceed the risks of therapy.

7. CONCLUSION

The optimal strategy for incorporating AIS into the adjuvant setting remains uncertain. The evidence reviewed in this article suggests that many postmenopausal women with early ER+ breast cancer who have completed 5 years of standard adjuvant tamoxifen have a significant risk of late breast cancer events and mortality. Nodal status is predictive of breast cancer events and of mortality from years 6 to 10 after diagnosis. Among node-negative patients, tumour size and grade are useful prognosticators.

When faced with treatment decisions regarding extended adjuvant letrozole for women who have completed 5 years of tamoxifen, physicians will find it helpful to estimate the absolute risk of breast cancer. Women at low risk of breast cancer events or death are those with low-grade node-negative disease; they are likely adequately treated with 5 years of tamoxifen alone. Notably, approximately 16% of all breast cancers are low-grade [2]. Women with nodal involvement or increasing T stage are at significant risk of relapse in the 5 years after tamoxifen. They are therefore potential candidates for extended adjuvant letrozole. For moderate-risk, node-negative patients, grade and tumour size are useful factors to incorporate into the estimation of breast cancer risk.

The optimal duration of letrozole therapy is difficult to determine, given that the NCIC MA-17 trial was unblinded at 2.4 years. In some Canadian provinces, 3 – 5 years of letrozole has been recommended (3 years in British Columbia, and more recently, 5 years in Ontario). That strategy will certainly be subject to ongoing review as new data continue to emerge, particularly with the further randomisation of selected MA-17 subjects to another 5 years of letrozole.

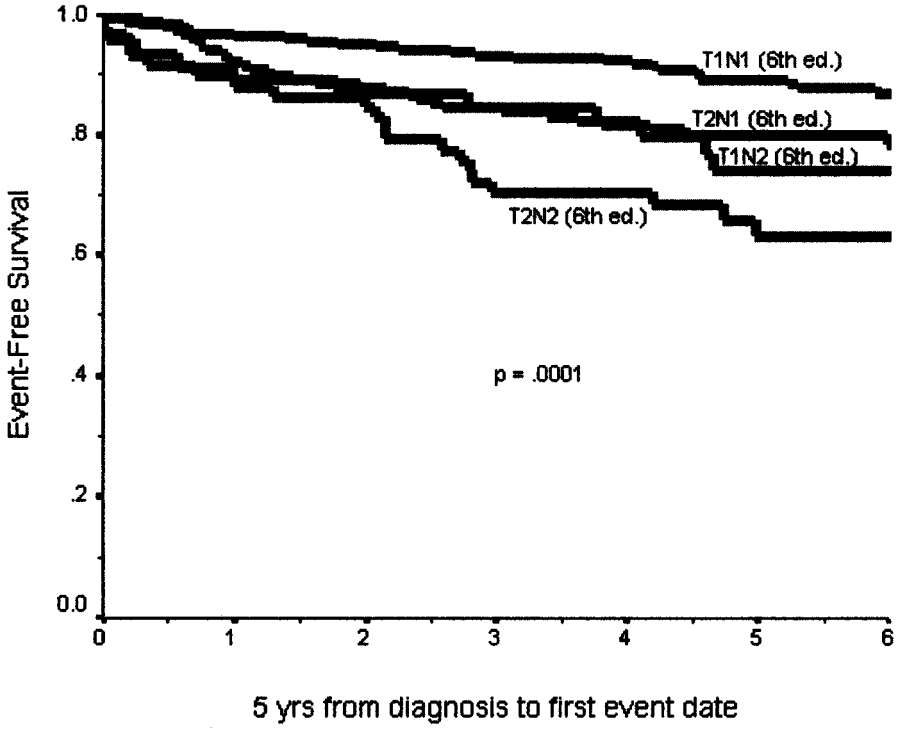

FIGURE 1 *Kaplan–Meier event-free survival (EFS) curves according to stage among postmenopausal oestrogen receptor–positive women treated with 5 years of tamoxifen [14]. Event-free survival was defined as absence of locoregional or distant recurrence, a new contralateral breast cancer, or breast cancer–related death [14]. T1 = <2-cm tumour; T2 = 2- to 5-cm tumour; N0 = 0 nodes positive; N1 = 1 – 3 nodes positive; N2 = 4 – 9 nodes positive [15].*

TABLE III Low-, moderate-, and high-risk groups of women after 5 years of adjuvant tamoxifen and recommended extended adjuvant therapy [a]

Breast cancer risk category	*Profile* [b]	*Recommendation*
Low (<5%)	T1 or 2 N0, grade 1	Extended therapy likely not indicated
Moderate (5%–15%)	T1 or 2 N0, grade 2/3	Consider for extended letrozole therapy [c]
High (>15%)	T any N1/N2	Consider for extended letrozole therapy [c]

[a] Adapted from: Headcan Health Education Media. Managing breast cancer recurrence risk [risk stratification instrument]. Toronto, ON: Headcan Health Education Media. [Available at: www.headcan.com; cited August 25, 2005]

[b] T1 = <2-cm tumour; T2 = 2- to 5-cm tumour; N0 = 0 nodes positive; N1 = 1 – 3 nodes positive; N2 = 4 – 9 nodes positive [15].

[c] Consider 5-year life expectancy and comorbidities, including osteoporosis risk, in individual risk–benefit assessment.

8. REFERENCES

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