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Original Article

Adherence to Adjuvant Endocrine Therapy in Christchurch Women with Early Breast Cancer

B. Robinson [*†‡], B. Dijkstra [§], V. Davey [§], S. Tomlinson [*], C. Frampton [‡]

[*] University of Otago Christchurch, Christchurch, New Zealand
[†] Oncology Service, Christchurch Hospital, Christchurch, New Zealand
[‡] Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand
[§] Department of General Surgery, Christchurch Hospital, Christchurch, New Zealand

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Abstract

Aims: To assess adherence to adjuvant endocrine therapy by a real-world cohort of women in Christchurch and to determine any associated factors.
Materials and methods: Records were retrieved of all women newly diagnosed with early breast cancer and registered on the Christchurch Breast Cancer Patient Register over 4 years from June 2009. Demographic and pathological factors, dates of starting and stopping endocrine therapies and reported side-effects were collected. The proportion remaining on endocrine therapy was analysed by Kaplan–Meier curve; Cox regression analysis was used to identify independent factors influencing adherence.
Results: Of 1213 women, 1018 (83.9%) had oestrogen receptor-positive tumours, of whom 674 (66.2%) started adjuvant endocrine therapy, including 62 (9.2%) neoadjuvantly. Uptake was 52.4% of those with T1 tumours, 89% with T2 tumours, 93% with T3/T4 tumours, 92.7% with node-positive tumours and 49.7% with node-negative tumours. The initial endocrine therapy was an aromatase inhibitor in 254 (38%) and tamoxifen for 412 (61%). At 1 year, 90% remained adherent, at 2 years 84%, at 3 years 81%, at 4 years 76%, at 4.5 years 71% and at 5 years 50%, with a median duration of 60 months (56–64 months, 95% confidence interval) and a median follow-up of 33 months. Overall, 135 (20%) women stopped treatment for adverse events or poor tolerability. A longer persistence with endocrine therapy was associated with node-positive tumours (hazard ratio 1.38, $P = 0.003$), but not first hormone used; aromatase inhibitor compared with tamoxifen, $P = 0.76$.
Conclusion: Adjuvant endocrine therapy use fell to 50% by 5 years, limiting possible survival benefits, providing support for efforts to increase compliance.

Key words: Adjuvant therapy; breast cancer; early stage; endocrine therapy; patient adherence

Introduction

New Zealand cancer survival was reported to lag behind that in Australia, and for breast cancer the gap widens with the number of years since diagnosis [1]. This has been interpreted to reflect similar rates of early diagnosis and mammographic screening, but probable differences in adjuvant chemotherapy and endocrine therapy. Women with early breast cancer that expresses oestrogen receptors are recommended for adjuvant endocrine therapy with aromatase inhibitors or tamoxifen for at least 5 years, as recurrence and survival outcomes are significantly improved [2]. A lack of adherence to adjuvant endocrine therapy is common, with a systematic review recording that 31–73% of women discontinue endocrine treatment before 5 years [3] and 52% stopped by 5 years in a Scottish study [4]. In randomised trials of adjuvant therapy, premature discontinuations ranged from 11 to 30% [5]. Discontinuations were higher for tamoxifen than aromatase inhibitors at 47.2% (confidence interval 41.1–53.5%) and 31.0% (confidence interval 25.9–37.5%), respectively, from a meta-regression analysis [6] of a meta-analysis [3], despite the relatively high incidence of arthralgias on aromatase inhibitors [7].

Adherence has two main components, whether the person is compliant with taking the tablets and how long

Author for correspondence: B. Robinson, Oncology Service, Christchurch Hospital, 1 Riccarton Avenue, Christchurch 8140, New Zealand. Tel: +64-33640361.
E-mail address: Bridget.robinson@cdhb.health.nz (B. Robinson).

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the therapy is continued [7,8] and medical and pharmacy records do not correlate closely [7,9]. For example, only three-quarters of women who reported compliance were taking more than 80% of their prescribed hormone therapy [10]. Early evidence for poorer survival for early discontinuation came from the Early Breast Cancer Trialists Collaborative Group [11], where tamoxifen for 5 years had a significantly greater survival benefit than shorter durations. The Scottish study showed poorer all-cause survival in the women with <80% adherence [4]. In New Zealand, the Waikato Breast Cancer Register has reported >80% compliance in 70% of women at 1 year, falling to 59% by 4 years with lower compliance in Maori, and found higher breast cancer mortality and more recurrences for poor adherence [12].

Our aim was to establish the level of adherence to adjuvant endocrine therapy by women in the Christchurch region. The objectives were to determine the rates of initiation of endocrine therapy for women with oestrogen receptor-positive cancers, correlate this with prognostic factors and to then determine the number of women continuing adjuvant endocrine therapy at each annual anniversary, and specifically for 5 years, and identify the reasons for discontinuation.

Materials and methods

All women diagnosed with a new breast cancer in the Christchurch region have been entered on the Christchurch Breast Cancer Patient Register since 2009 [13]. The data were retrieved for all those diagnosed with their first invasive breast cancer over a 4 year period, between June 2009 and June 2013, who had oestrogen receptor-positive tumours, with no distant metastases at diagnosis. Exclusions were women with a pre-existing invasive breast cancer and 20 women who declined to be on the register. New data fields relevant to endocrine therapies were added to the register. For those who were started on neoadjuvant or adjuvant endocrine therapy, details about first and subsequent therapies used, medical adverse events and side-effects were sought, with start and stop dates for each endocrine therapy. All changes or interruptions in endocrine therapy, and reasons for this, whether temporary or permanent, together with side-effects, were regularly updated on to the register from a review of the electronic medical records. Body mass index (BMI) and Charlson morbidity score at diagnosis [14] were calculated for each woman. The date of last follow-up and disease status at that time were recorded.

The women were treated following current New Zealand guidelines, with wide local excision or mastectomy, then consideration of adjuvant systemic therapy following discussion in the breast multidisciplinary meeting. Radiological staging was reserved for those with a high risk of systemic spread: those with locally advanced cancers or those with more than four nodes involved or large tumours or a suspicious finding on history and examination. Women with locally advanced cancer started chemotherapy and/or endocrine therapy before surgery (neoadjuvant) and then continued endocrine therapy adjuvantly. When given, adjuvant chemotherapy preceded endocrine therapy and radiation therapy. Adjuvant endocrine therapy was started at the completion of radiation, following the oncology service guideline. Patients were followed initially 3 monthly and then 6 monthly, by members of the breast team, with efforts made to support continuing endocrine therapy for 5 years. The data for the 11 women who became lost to follow-up are included and censored at their last assessment date. Uptake of adjuvant endocrine therapy was determined according to nodal status and tumour size. Data about smoking status, assessment of bone mineral density (BMD) and the start of bone-protecting therapies were accessed from the medical records. Referrals for psychosocial support while on endocrine therapy were documented.

The data were analysed using Kaplan–Meier curves to estimate the proportion remaining on endocrine therapy over time. Cox regression analysis was used to identify factors independently influencing the continuation of endocrine therapy. Side-effects on aromatase inhibitors and tamoxifen were compared using the chi-square test.

Results

Over the 4 year study period, 1213 women were diagnosed with new non-metastatic breast cancer, of whom 1018 (83.9%) had oestrogen receptor-positive tumours and 184 (15.2%) had oestrogen receptor-negative tumours, with 11 (0.9%) unknown. Table 1 shows the uptake of adjuvant (and neoadjuvant) endocrine therapy by tumour T stage and nodal status, for those with oestrogen receptor-positive cancers. Endocrine therapy was started before or used instead of surgery in 62 women, including 47 women aged older than 80 years, of whom nine underwent surgery to the primary tumour. Overall, two-thirds of the women ($n = 674$; 66.1%) started adjuvant endocrine therapy, either as neoadjuvant therapy ($n = 62$; 9.2%) or as post-surgical adjuvant therapy ($n = 612$; 57%). The remaining 346 women did not start endocrine therapy, with 3.5% not referred because of low benefit and the remainder who were referred evenly distributed between a shared decision of insufficient benefit and of declining therapy. Uptake of adjuvant endocrine therapy was higher for larger tumours and nodal involvement.

Considering the group who started adjuvant endocrine therapy, 50% of the women had tumours less than 20 mm (T1) in size, 40% had T2 tumours (20–50 mm) and 10% had T3 or T4 tumours. Their tumour grade was intermediate or high in 89% and nodes were not involved in 47%. Most (92%) had primary surgery; 40% received adjuvant chemotherapy, with neoadjuvant chemotherapy being used in 35 women.

The characteristics of the 674 women who started adjuvant endocrine therapy are shown in Table 2. The median age of this cohort was 58 years; 36% were premenopausal and 61% were postmenopausal. The stated ethnicity was New Zealand/European for 89.4%, Maori for 5.5%, Asian 3.0% and Pacific 1.5%. BMI was known for 78% of the women and was approximately equally divided into one-third

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Table 1
Use of adjuvant endocrine therapy for all 1020 women diagnosed with a new breast cancer in the 4 year period with oestrogen receptor-positive tumours, according to tumour size, nodal status and tumour grade

	Total	Endocrine therapy (*n*)	Endocrine therapy (%)
T1	646	338	52.3
T2	302	269	89.1
T3,4	70	65	93
Unknown	2	2	
Node-negative	632	313	49.5
Node-positive	330	306	92.7
No axillary surgery	60	55	91.7
Grade 1	196	74	37.8
Grade 2	467	328	70.2
Grade 3	295	266	90.2
Grade unknown	62	6	9.8
Total	1020	674	66.1

Table 2
Demographic characteristics of the 674 women with oestrogen receptor-positive cancers who started adjuvant and/or neoadjuvant endocrine therapy

Characteristic	Subgroup	*n*	%
Age	<56 years	295	43.8
	56–65 years	170	25.2
	>65 years	209	31.0
Ethnicity	New Zealand/European	601	89.4
	Maori	37	5.5
	Asian	20	3.0
	Pacific	10	1.5
	Other	4	0.6
Menopausal status	Pre-/perimenopausal	246	36.5
	Postmenopausal	414	61.4
	Unknown	14	2.1
Body mass index (kg/m^2)	<18.5, underweight	7	1.0
	18.5–24.99, normal	168	24.9
	25–29.99, overweight	174	25.8
	>29.99, obese	178	26.4
	Unknown	147	21.8
Charlson morbidity score	0	487	72.3
	1	128	19.0
	2	41	6.1
	3	18	2.7
Polypharmacy	<4 medications	549	81.5
	4 or more medications	123	18.2
	Unknown	2	0.3
Smoker	Current	80	11.9
	Ex-smoker	152	22.6
	Never	398	59.1
	Unknown	44	6.5

normal, one-third overweight and one-third obese. Significant comorbidity was present in 28%, as assessed from the Charlson score [14]; 18% were using more than four regular medications. There were 12% who were current smokers and 23% were ex-smokers.

The initial endocrine treatment received by the 674 women was an aromatase inhibitor in 254 (38%) and tamoxifen for 412 (61%), whereas 11 started on goserelin, eight as a single agent, one concurrently with an aromatase inhibitor and two with tamoxifen. The initial aromatase inhibitor used was anastrozole, 134 women, letrozole ($n = 110$) and exemestane ($n = 10$).

Adherence to adjuvant endocrine therapy was assessed using the Kaplan–Meier estimate for the proportion who remained on continuous endocrine therapy, whether or not they switched medication (Figure 1). Patients were censored if they had recurrent or metastatic disease, were deceased, or lost to follow-up (11 women). At 1 year, 90% remained adherent, at 2 years 84%, at 3 years 81%, at 4 years 76%, at 4.5 years 71% and at 5 years 50%. This suggests an increase in discontinuations in the last 6 months of the 5 years. The median duration of endocrine therapy was 5 years or 60 months (56–64 months, 95% confidence interval). The median follow-up was 33 months.

At last follow-up, 257 of the 674 women had stopped endocrine therapy, 37% of them for recurrence, development of metastases or death, whereas 10.5% had completed adjuvant therapy (including three who remained on treatment more than 5 years). Half (52.5%) of the women had stopped endocrine therapy for adverse events or side-effects, comprising 20% of the whole cohort. BMD was measured in 281 women (41.8%), either initially or on follow-up; including 63.3% of those starting an aromatase inhibitor and 30.2% starting tamoxifen.

Cox regression analysis was carried out to determine the impact of clinicopathological variables on the length of time women remained on endocrine therapy, in the absence of recurrence. The Nottingham Prognostic Index [15] was significant ($P = 0.004$), but not available for all patients, whereas tumour size (T stage) and nodal status were also significant at $P = 0.04$ level. Tumour grade, no primary surgery, adjuvant chemotherapy, age, menopausal status, ethnicity, BMI, polypharmacy, Charlson score [14] and smoking were not associated.

Node-positive tumours were associated with longer persistence with endocrine therapy (hazard ratio 1.38, $P = 0.003$), with a median duration of endocrine therapy of 62 months for women with node-positive tumours compared with 60 months for node-negative tumours. For node-positive tumours, 79% of women remained on endocrine therapy at 54 months and 63% at 60 months compared with 63% and 44%, respectively, for node-negative women ($P = 0.003$, Kaplan–Meier curve not shown). Higher tumour stage, T2–4 stages combined, compared with T1, was associated with a longer duration of endocrine therapy ($P = 0.012$), but once adjusted for nodal status this became only marginally significant.

There was no association of adherence with the first hormone used, aromatase inhibitor compared with tamoxifen, $P = 0.76$. For those starting with an aromatase inhibitor, 67 changed therapy, 39 to a different aromatase inhibitor and 28 to tamoxifen. For those starting with tamoxifen, 141 switched to an aromatase inhibitor. This included 56 who had a planned switch after 2–3 years. At

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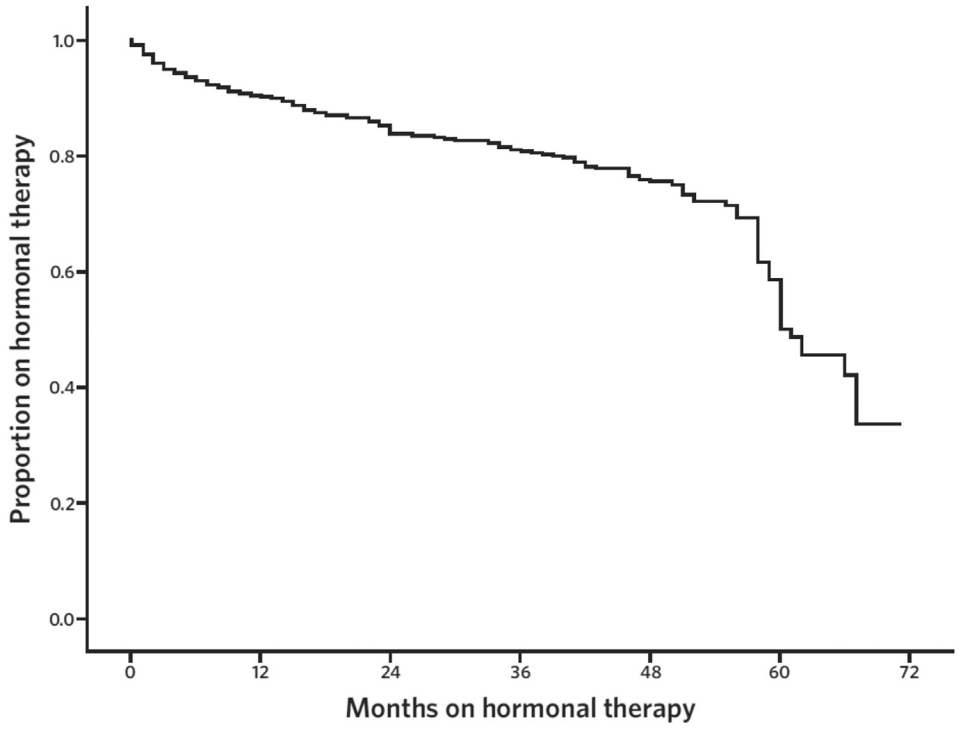

Fig 1. Proportion of all women who remained on adjuvant endocrine therapy according to calendar months since neoadjuvant or adjuvant therapy started. Includes all 674 women who started endocrine therapy, whether or not they changed to an alternative medication, with the final date they ceased any endocrine therapy. Numbers at risk at 12 months, 572; 24 months, 445; 36 months, 274; 48 months 147, 54 months, 102; 60 months, 37.

last follow-up, 60.2% who had started on an aromatase inhibitor and 63.1% who had started tamoxifen continued therapy. The median time of being on the first hormone was 3.3 years or 40 months (34–46 months, 95% confidence interval). After a second hormone, 59 women went on to a third hormone, with 30 women starting an aromatase inhibitor; 10 tamoxifen, 17 restarting their previous hormone and three starting goserelin (two alone, one concurrently).

To better understand the reasons for stopping an endocrine therapy, events during treatment with the first endocrine therapy were explored in more detail. Side-effects and adverse events reported by 666 women receiving an aromatase inhibitor or tamoxifen as their initial endocrine therapy are shown in Table 3. Only the one side-effect or adverse event that led to stopping that endocrine therapy is reported for each woman. Arthralgia ($P < 0.001$) and a decrease in BMD ($P < 0.01$) were more likely for the aromatase inhibitors, whereas flushes ($P < 0.01$) and gynaecological symptoms, including vaginal bleeding ($P < 0.01$), were more likely with tamoxifen. Mood changes and thrombosis were not significantly different. The proportion of women who stopped their first endocrine therapy for side-effects or adverse events was similar for aromatase inhibitors (29.5%) and tamoxifen (31.8%). One of the eight women on goserelin alone reported depression.

It was anticipated that mood and psychological symptoms might influence adherence. Records showed that 85 women had psychological symptoms at diagnosis and 99 women had past psychological issues, and all but one in each case persisted with endocrine therapy. After diagnosis, 38 women were referred to psychological services, with 35 of them persisting with hormonal therapy. Eighteen were referred to menopausal specialists.

Discussion

Persistence with adjuvant endocrine therapy steadily declined over time in women receiving adjuvant endocrine therapy for early breast cancer in Christchurch, with the greatest decrease after 4 years of therapy. This shows the need for clinicians to emphasise the importance of persistence until the end of the planned 5 years of therapy. Side-effects were the main reason for discontinuation, suggesting that managing side-effects is probably important in gaining the most benefit from the therapy. Predominant side-effects were arthralgia and joint problems, and low BMD for aromatase inhibitors, flushes and gynaecological problems for tamoxifen, and mood changes. Women switched between endocrine therapies, some planned, from tamoxifen to an aromatase inhibitor, but others to seek a better tolerated agent. There was a significant association of node-positive status, as well as Nottingham Prognostic Index, with a longer duration of endocrine therapy, which may reflect greater efforts to sustain treatment on the part of the clinicians and patients for poorer risk cancers. Clinicians determined BMD more frequently for those starting aromatase inhibitors.

These results are similar to those from other countries, including France, with 31% non-persistent at 5 years in a

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Table 3
Side-effects and adverse events that resulted in cessation of the first endocrine therapy for 666 women who started an aromatase inhibitor or tamoxifen. Each patient is listed once, with their most significant event

First endocrine therapy	Aromatase inhibitor		Tamoxifen	
Number starting therapy	254		412	
	Side-effects/adverse events	%	Side-effects/adverse events	%
Flushes	3	1.1	22	5.3
Arthralgia, joint pain	28	11.0	6	1.5
Gynaecological symptoms, bleeding	1	0.4	19‡	4.6
Decrease bone mineral density	5	2.0		
Mood changes, depression	4*	1.6	18§	4.4
Other symptoms	6	2.4	9	2.2
Weight gain, swelling	1	0.4	4	1.0
Cardiovascular	2†	0.8	3‖	0.7
Thromboembolism			5¶	1.2
Rash, allergy, drug reaction	2	0.8	8**	1.9
Not tolerated, not otherwise specified	22	8.7	36	8.7
Non-compliant	1	0.4	1	0.2
Total stopped due to drug effects	75	29.5	131	31.8

Adverse events included: *1 depression; †1 hypertension; 1 visual change; ‡7 uterine bleeding; §2 depression; ‖1 transient ischaemic attack; 2 cerebrovascular events; ¶3 deep venous thrombosis; 2 pulmonary embolism; **1 myositis; 1 hyponatraemia.

study of 600 women, 6% of whom, however, had metastases [16]. They are similar to the other published New Zealand experience from Waikato with 59% adherent at 4 years [12]. Notably, however, our study showed a sharp fall in adherence after 4.5 years, suggesting a relaxation of recommendation by clinicians at that time, with a fall from 71% persisting at 4.5 years to 50% at the 5 year mark. The data in this real-world cohort are similar to randomised trials, such as the BIG 1-98 trial, in that side-effects were the main reason for stopping adjuvant endocrine therapy in the BIG 1-98 trial [17], accounting for 82.7% of discontinuations. The cohort, however, predates guidelines recommending dual therapy including ovarian suppression for premenopausal women with high-risk disease, which may be poorly tolerated [18].

The strengths of this study are the prospective registration of virtually all women treated for breast cancer in Christchurch during the study period, due to the breast cancer register [13]. The patients were homogeneous in all receiving adjuvant therapy for early breast cancer and any with metastatic disease were excluded. In addition, the register had systematically recorded details about each endocrine treatment and reasons for changes, which was augmented by a further search of electronic clinical records. Potential weaknesses were the inability to access all the pharmacy records to determine whether women filled their prescriptions and prospective assessment of compliance, the retrospective review of the registry data and lack of quality of life data. The determination of recurrence risk was relatively broad, using nodal status, tumour grade and tumour size, rather than an online tool with continuous variables. Follow-up is still relatively short, but 20% had already stopped for side-effects. The total study cohort, even though it comprises nearly 700 women, is probably too small for future determination of differences in recurrence or survival by adherence.

No particular group of patients could be identified who were at increased risk of early discontinuation, other than those with smaller or node-negative tumours. Prior chemotherapy did not increase non-persistence, in contrast to the French study of a similar number of women, which included women with metastatic disease [16]. Older age, smoking and prior thrombotic event have been associated with reduced adherence, in addition to node negativity, as in this study [17]. A survey of women in Detroit and Los Angeles who started endocrine therapy found that of those who stopped early, 40% stopped for side-effects, 25% cited worry about risks and 23% disliked taking medication [19]. Women who reported greater symptoms and had poorer communication with their clinician were found to be more likely to stop their endocrine therapy whether intentional or unintentional [20].

Our breast service has followed traditional outpatient clinic follow-up practices, with a review of the side-effects of endocrine therapy by the breast nurse or doctor. During the study period, practice-changing data were maturing about extended adjuvant therapy [2,17,21,22], but were not consistently discussed with women in the earlier years. Resource constraints and the established benefit of extended adjuvant endocrine therapy [17,21,22] mandate novel approaches to enhance adherence. Although provision of educational materials in the Patient's Anastrozole Compliance to Therapy (PACT) trial did not improve adherence [23], the COMPAS trial showed that sending reminder letters and/or telephone calls increased adherence for aromatase inhibitors [24].

Conclusions

This study showed that half the women stopped their endocrine therapy before the planned 5 years, which is

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associated with poorer outcomes [5,7,11,17], with 20% stopping for poor tolerability. The women studied represent a real-world population, so are relevant to usual clinical practice. The reported gap between breast cancer survival for women with breast cancer in Australia and New Zealand increased over time, especially after 5 years, and has been associated with increased use of chemotherapy and hormonal therapy in Australia compared with New Zealand [25]. As extending adjuvant endocrine therapy beyond 5 years improves outcomes for both tamoxifen and aromatase inhibitors [17,21,22], those women who discontinue adjuvant endocrine therapy prematurely before 5 years not only derive less benefit, but they also do not go on to access beneficial extended adjuvant endocrine therapy. This study offers support for the need to develop interventions such as reminder letters or telephone calls to enhance persistence rates, especially when patients reach the later years of adjuvant endocrine therapy.

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