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EDITORIAL

The value-for-money of adjuvant aromatase inhibitors: time to put the debate to rest?

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The adoption of costly treatments in public health care systems, such as exists in Canada, must take into account their "clinical benefit to side effect" profiles and "value for money" in an attempt to maximize health gains within current budget constraints.

Postmenopausal women with early-stage endocrine-sensitive breast cancer benefit largely from adjuvant endocrine therapy with tamoxifen (TAM) or aromatase inhibitors (AIs)[1]. The current strategies of adjuvant endocrine therapy for postmenopausal women include TAM alone for 5 or 10 years and several AI-containing strategies: sequential TAM–AI for 5 years (that is, TAM for 2–3 years, followed by AI for 3–2 years) and vice versa, upfront AI for 5 years, and extended AI for 5 years after initial 5-year therapy with TAM[1].

Overall, compared with 5-year TAM treatment alone, the AI-containing strategies have consistently been associated with improvements in disease-free survival and, in some instances, overall survival[1]. In a large meta-analysis by the Early Breast Cancer Trialists' Collaborative Group[2], upfront AI, compared with TAM alone, was associated with an absolute 2.9% [standard error (SE): 0.7%] decrease in recurrence (9.6% for AI vs. 12.6% for TAM, $2p < 0.00001$) and an absolute nonsignificant 1.1% (SE: 0.5%) decrease in breast cancer mortality (4.8% for AI vs. 5.9% for TAM, $2p = 0.1$) at 5 years' follow-up. Sequential AI after 2–3 years of TAM, compared with TAM alone, was also associated with an absolute 3.1% (SE: 0.6%) decrease in recurrence (5.0% for AI vs. 8.1% for TAM after divergence, $2p < 0.00001$) and an absolute 0.7% (SE: 0.3%) decrease in breast cancer mortality (1.7% for AI vs. 2.4% for TAM, $2p = 0.02$) at 3 years after treatment divergence (that is, approximately 5 years after the start of hormonal therapy). in the absence of contraindications or intolerance to AIs, Current clinical practice guidelines generally recommend an AI-containing strategy for postmenopausal women with endocrine-sensitive disease; however, the optimal AI strategy remains unknown[1]. Head-to-head comparisons of upfront AI with sequential TAM–AI in the Breast International Group 1-98 and TEAM trials did not reveal statistically significant differences in disease-free survival or overall survival among the AI-containing strategies examined[1].

Economic evaluations, including cost-effectiveness and cost–utility analyses, have become a pivotal component in the overall assessment of oncologic therapies or interventions that are being considered for funding in public health care systems. A number of Canadian cost–utility analyses have examined the incremental upfront drug acquisition costs associated with AIs ($41–$161 monthly) and with TAM ($10.50 monthly) within the context of all potential treatment-related benefits and adverse events (Table I)[3–4]. In those analyses, the relative benefits associated with various adjuvant endocrine strategies were obtained directly from the relevant clinical trials or derived indirectly through network meta-analyses in the absence of head-to-head comparisons between certain strategies. Overall, compared with 5-year TAM alone, all AI strategies examined (upfront, sequential, and extended) appear to provide good value for money when judged against the commonly-used North American willingness-to-pay thresholds of $50,000–$100,000 per quality-adjusted life-year gained. In the analyses based on drug acquisition costs of $148–$161 per month for patented AI brands, AI strategies were associated with cost-effectiveness ratios between $13,006 and $38,703 per quality-adjusted life-year gained.

Interestingly, compared with upfront AI, sequential TAM–AI appeared to be the economically favourable strategy in two evaluations by Skedgel *et al.*[8] and Younis *et al.*[9], which involved indirect network meta-analyses before results of the TEAM and Breast International Group 1-98 sequential strategies became available. In the former two evaluations, upfront AI did not appear to be a cost-effective strategy relative to sequential TAM in most scenarios examined. In a more recent analysis based on the generic AI brand cost ($41 monthly), which also involved a network meta-analysis, the 5-year

TABLE I Canadian cost-effectiveness evaluations of adjuvant aromatase inhibitors (AIs)

Reference	*Endocrine strategy*	*Cost/QALY gained*[a]
Rocchi and Verma, 2006[5]	Upfront AI (anastrozole) vs. tamoxifen	28,000
El Ouagari *et al.,* 2007[6]	Extended AI (letrozole) vs. tamoxifen	34,058
Risebrough *et al.,* 2007[7]	Sequential tamoxifen→AI (exemestane) vs. tamoxifen	24,185
Skedgel *et al.,* 2007[8]	Upfront AI (anastrozole) vs. tamoxifen	38,703
	Sequential tamoxifen→AI (exemestane) vs. tamoxifen	13,006
	Upfront AI (anastrozole) vs. sequential tamoxifen→AI (exemestane)	114,638
Younis *et al.,* 2007[9]	Upfront AI vs. sequential tamoxifen→AI	Variable[b]
Delea *et al.,* 2008[10]	Extended AI (letrozole) vs. tamoxifen	23,662
Erman *et al.,* 2014[11]	Extended AI (letrozole) vs. extended tamoxifen	3,402

[a] Costs are in Canadian dollars, as reported in the relevant publications.
[b] Sequential tamoxifen→AI was the preferred cost-effective strategy at low and average relapse risk; upfront AI was cost-effective at very high relapse risk.
QALY = quality-adjusted life-year.

extended AI strategy (5 years of AI after 5 years of TAM), compared with the 5-year extended TAM strategy (10 years total of TAM), was associated with a favourable cost-effectiveness ratio of $3,402 per quality-adjusted life-year gained[11].

In this issue of *Current Oncology,* Djalalov *et al.*[12] examine the cost-effectiveness of various 5-year endocrine therapy strategies (upfront AI, sequential TAM–AI, sequential AI–TAM, and TAM alone) for postmenopausal women with breast cancer. Their analysis is based on the generic AI brand acquisition cost ($41 monthly) and an indirect network meta-analysis that incorporated relative treatment benefits from relevant clinical trials. Not surprisingly, the upfront and sequential TAM–AI strategies were both shown to provide good value for money compared with TAM alone, but with improved cost-effectiveness estimates relative to those previously reported based on the patented AI brand costs (Table I). In Djalalov *et al.,* both AI strategies were more effective and less costly than TAM alone (that is, they were dominant strategies), rather than being more effective and more costly, but having favourable cost-effectiveness estimates, as in earlier evaluations. Perhaps more importantly, Djalalov *et al.* also found that, compared with upfront AI, sequential TAM–AI (and possibly AI–TAM) is the economically preferred, cost-effective strategy, even with the recent drop in the drug acquisition costs related to AIs.

The choice of the optimal AI-containing endocrine strategy for postmenopausal women with breast cancer—whether upfront AI or sequential TAM–AI—should take into account the clinical benefits and side effects of both TAM and AI in various clinical scenarios, and individual patient preferences. However, from an economic perspective, compared with upfront AI, sequential TAM–AI (or AI–TAM) appears to be the economically preferred adjuvant endocrine strategy that can maximize health gains in the Canadian public health care system at expenditures within favourable value-for-money thresholds.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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