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ORIGINAL ARTICLE

Robin Murray

Role of anti-aromatase agents in postmenopausal advanced breast cancer

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Abstract *Purpose*: Endocrine therapy is a well-recognized approach to the treatment of postmenopausal patients with advanced breast cancer, particularly those with estrogen receptor-positive tumors. The availability of anti-aromatase agents, both reversible (nonsteroidal) and irreversible (steroidal), provides clinicians with additional hormonal treatment options. *Methods*: A MEDLINE search was conducted to identify studies that evaluated anti-aromatase therapy in the treatment of postmenopausal women with advanced breast cancer. In selecting studies, priority was given to randomized, controlled trials. *Results*: Tamoxifen is the standard first-line therapy for advanced breast cancer. However, recent results have demonstrated the efficacy of newer anti-aromatase agents in this setting. Among patients who have progressed after tamoxifen therapy, anti-aromatase agents have emerged as first choice therapy based on their better tolerability and improved efficacy compared with megestrol acetate. Exemestane and anastrozole (irreversible and reversible anti-aromatase agents, respectively) have demonstrated survival benefits over megestrol acetate in second-line therapy. Anti-aromatase agents have also demonstrated efficacy in patients who have failed multiple hormonal therapies. Based on these data, an algorithm for the treatment of postmenopausal women with advanced breast cancer is proposed. *Conclusions*: The enhanced tolerability and superior efficacy of anti-aromatase inhibitors compared with megestrol acetate has resulted in these agents becoming the endocrine treatment of choice for women with advanced breast cancer who have progressed after tamoxifen treatment. The increased use of tamoxifen in the adjuvant setting and the demonstrated activity of aromatase inhibitors in first-line therapy will further increase the role of these agents.

Keywords Postmenopausal breast cancer · Hormone therapy · Anti-aromatase agents

R. Murray
Peter MacCallum Cancer Institute,
St. Andrew's Place, East Melbourne 3002,
Australia
E-mail: robmurr@ozemail.com.au
Tel.: +61-3-96561111
Fax: +61-3-98241964

Introduction

Although there have been new developments in the treatment of metastatic breast cancer over the past few years, the disease still presents an important challenge for physicians. Current treatment strategies provide substantial palliation of symptoms, but have limited impact on survival and are often associated with objectionable side effects. Due to the large variety of clinical manifestations, a number of therapeutic modalities are used in treating advanced disease. Chemotherapy, hormonal therapy, surgery, and radiation therapy are all components of a metastatic breast cancer treatment strategy and, in general, are all utilized at some point during the course of the disease. Hormone therapy has long been accepted to be amongst the most successful treatments for breast cancer and a majority of postmenopausal patients presenting with metastatic disease will benefit from some form of endocrine therapy.

The availability of the anti-aromatase therapies, a novel class of estrogen-deprivation agents, offers clinicians a more selective approach to the hormonal treatment of breast cancer. The enhanced efficacy and tolerability of this approach have been demonstrated – several of these agents exhibit a survival advantage over current standard second-line therapy [5, 17]. The availability of anti-aromatase agents with different mechanisms of action now extends even further the range of effective agents from which a physician can select. Although the most effective sequence or combination in which to use these agents has yet to be elucidated, it is clear that these agents will play a major role in the future treatment of postmenopausal patients with metastatic breast cancer.

Establishing the course of treatment

For a postmenopausal woman presenting with metastatic disease, the initial decision regarding the course of treatment is based on a number of well-defined prognostic factors (Fig. 1) [11, 13]. Local therapy (e.g. surgery, radiation therapy) is beneficial in patients with a single focus of symptomatic disease or in the event of local crisis (impending fracture, spinal cord compression). Systemic therapy is first-line treatment for patients with multiple sites of recurrence and/or visceral disease not easily treated by local therapy. The choice between hormone therapy and chemotherapy is based on a set of patient factors including hormone receptor status, disease-free interval, age, and quality of life determinants [12].

Chemotherapy is the treatment of choice for hormone receptor-negative tumors, rapidly progressing visceral lesions, or tumors that have become refractory to hormonal treatment [10, 12, 13]. However, the significant toxicity of this approach is a major drawback, even with the advent of hematopoietic growth factors and better antiemetics. In addition, repeated use of chemotherapy following an initial treatment failure has limited effect on survival. Hormone therapy is the first choice of treatment for women who have limited and non-life-threatening disease, especially those with no

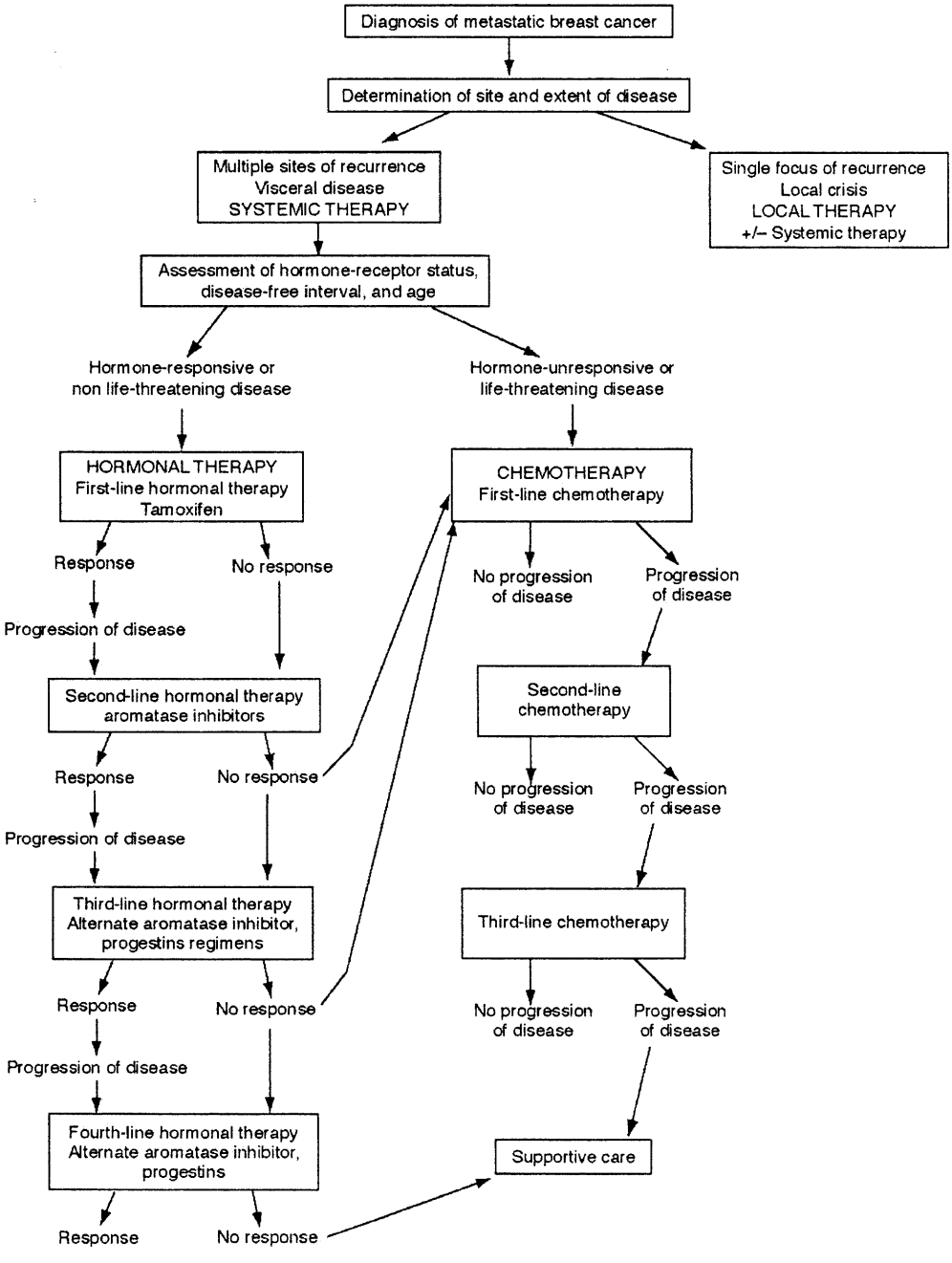

Fig. 1 Treatment algorithm for advanced postmenopausal breast cancer

symptoms, who are elderly, or who have estrogen receptor-positive tumors [11, 13]. Response rates to endocrine treatment can be as high as 60% to 70% in patients with high estrogen receptor levels [1] and the median duration of response is 9 to 12 months [27]. In contrast to chemotherapy, patients who initially respond and then become resistant to first-line hormone therapy often respond to second- or third-line endocrine interventions.

Treatment options for hormone-dependent disease

Hormonal agents used in the treatment of postmenopausal women with advanced breast cancer can be categorized by their mechanism of action (Table 1) [18]. The first hormonal anticancer agents developed to inhibit the growth-stimulatory effects of estrogen were antiestrogens. Antiestrogens compete with estrogen for binding to its receptor, inhibiting the cascade of estrogen receptor-mediated events in estrogen receptor-positive patients. Tamoxifen, the prototype antiestrogen, is associated with a greater response rate and fewer side effects than chemotherapy and is the first choice of hormone therapy. However, resistance to tamoxifen eventually develops, resulting in disease progression and the need for other therapeutic options. The increasing use of tamoxifen in the adjuvant setting, compounded by the cross-resistance observed with other antiestrogens, has further increased the demand for alternate hormonal agents for metastatic disease.

Estrogen deprivation is another hormonal strategy that has shown a great deal of promise in the treatment of breast cancer. By selectively inhibiting aromatase, the final rate-limiting step in estrogen biosynthesis, circulating levels of estrogen can be minimized and estrogen-dependent tumor growth inhibited [3]. Two classes of anti-aromatase agents have been identified that differ in the site and mechanism by which they bind aromatase. Reversible (nonsteroidal) anti-aromatase agents (aminoglutethimide, anastrozole, fadrozole, letrozole) bind competitively to the heme region of the protein. In contrast, irreversible (steroidal) anti-aromatase agents (formestane, exemestane) bind irreversibly to the substrate binding site, thereby inactivating the enzyme. With steroidal aromatase inactivators, recovery of full enzymatic potential requires de novo synthesis of the enzyme, which may explain the novel pharmacodynamic profile of these agents. Anti-aromatase agents have demonstrated efficacy in all stages of treatment of postmenopausal patients with metastatic breast cancer and are better tolerated than standard second-line therapies (e.g. megestrol acetate).

Table 1 Hormonal agents used in the treatment of advanced breast cancer

Antiestrogens	
Steroidal	Tamoxifen
	Fulvestrant (investigational)
Nonsteroidal	Droloxifene (investigational)
	Toremifene
Anti-aromatase agents	
Irreversible inactivators	Formestane (approved in Europe)
	Exemestane
Reversible inhibitors	Aminoglutethimide
	Anastrozole
	Fadrozole (approved in Japan)
	Letrozole
Progestins	Megestrol acetate
	Medroxyprogesterone acetate
Progesterone antagonists	Mifepristone (investigational)

Efficacy of anti-aromatase agents

First-line hormonal therapy

Tamoxifen is first-line therapy for advanced breast cancer in postmenopausal women and the benchmark against which all other agents are measured (Fig. 1). Two early anti-aromatase agents (fadrozole and formestane) have been assessed as first-line therapy and, although tolerability is enhanced, they do not demonstrate superior efficacy when compared with tamoxifen (Table 2) [6, 9, 29].

Recently, newer reversible (letrozole and anastrozole) and irreversible (exemestane) anti-aromatase agents have been compared with tamoxifen as first-line therapy and initial results have been published (Table 2). Two trials have compared anastrozole to tamoxifen in patients who had never received tamoxifen or who had completed tamoxifen therapy more than 12 months previously [2, 23]. In the North American trial involving 353 patients, anastrozole 1 mg/day produced an overall success in significantly more patients than tamoxifen 20 mg/day (59% vs 46%, $P = 0.0098$) [23]. The median time to progression was also significantly longer in the anastrozole group (11.1 months) than in the tamoxifen group (5.6 months, $P = 0.005$). However, in a larger European trial ($n = 668$) there was no significant difference between anastrozole and tamoxifen in terms of objective response (33% vs 33%, respectively), clinical success (56% vs 56%), or time to progression (8.2 vs 8.3 months) [2]. Both treatments were well tolerated, but anastrozole was associated with fewer thromboembolic and vaginal bleeding events than tamoxifen [2, 23].

In patients who had not received prior endocrine therapy (except adjuvant) letrozole 2.5 mg/day produced significantly longer time to progression (9.5 months) compared with tamoxifen 20 mg/day (5 months, $P = 0.0001$) [20]. Preliminary results from a randomized phase II trial indicate that exemestane 25 mg/day has efficacy at least as good as that of tamoxifen 20 mg/day in the first-line setting [24]. Among 63 evaluable patients, exemestane was associated with a higher overall response (42% vs 16%) and overall success (58% vs 31%) rates and a longer time to progression (8.9 vs 5.2 months) compared with tamoxifen [24].

Table 2 Efficacy of anti-aromatase agents in advanced postmenopausal breast cancer (*NR* not reached, *NS* no significant difference)

Therapy	Drugs compared	Reference	Objective Response (%)	Duration of Response (months)	Overall success (%)[b]	Time to treatment failure (months)	Time to tumor progression (months)	Median survival (months)	Serious adverse drug reactions (%)
First-line therapy	Fadrozole 1 mg twice daily vs tamoxifen 20 g/day	10	20 vs 27	15 vs 20			6.1 vs 8.5 ($P < 0.05$)		
		29	43 vs 48	11 vs NR ($P = 0.009$)		5.1 vs 5.4	5.4 vs 5.2	26 vs 34 ($P = 0.046$)	
	Formestane 250 mg every 2 weeks vs tamoxifen 30 mg/day	6	33 vs 37	15 vs 20		6.6 vs 9.8 ($P < 0.005$)	7.1 vs 9.8 ($P = < 0.01$)	35 vs 38	
	Letrozole 2.5 mg/day vs tamoxifen 20 mg/day	20					9.5 vs 5 ($P = 0.0001$)		
	Anastrozole 1 mg/day vs tamoxifen 20 mg/day	2	21 vs 17	16.5 vs 14.5	59 vs 46 ($P = 0.0098$)		11.1 vs 5.6 ($P = 0.005$)		
		23	33 vs 33		56 vs 56		8.2 vs 8.3		
	Exemestane 25 mg/day vs tamoxifen 20 mg/day	24	42 vs 16		58 vs 31		8.9 vs 5.2		
Second-line therapy	Aminoglutethimide	21	37	12.5	44				
	Anastrozole 1 mg/day vs megestrol acetate 40 mg four times daily	5	13 vs 12		42 vs 40		4.8 vs 4.6	27 vs 23[c] ($P < 0.025$)	6.1 vs 9.1
		15	14 vs 13	9 vs 9	34 vs 33	4.0 vs 3.8	4.4 vs 4		
	Fadrozole 1 mg twice daily vs megestrol acetate 40 mg four times daily	4	11 vs 16				3.7 vs 3.8		
			13 vs 11	NS		NS	NS	NS	
	Letrozole 2.5 mg/day vs megestrol acetate 160 mg/day	8	24 vs16 ($P = 0.04$)	33 vs 18 ($P = 0.002$)	35 vs 32	5.6 vs 5.5 ($P = 0.05$)	5.1 vs 3.9 ($P = 0.02$)	25.3 vs 21.5	10 vs 29
	Formestane 250 mg every 2 weeks vs megestrol acetate 160 mg/day	26	16 vs 20				5.8 vs 6.3		
		30	17 vs 17		39 vs 39				24 vs 33
	Exemestane 25 mg/d vs megestrol acetate 40 mg four times daily	17	15 vs 12		37 vs 34	3.8 vs 3.7 ($P = 0.042$)	5 vs 4 ($P = 0.037$)	NR vs 29 ($P = 0.039$)	7.6 vs 17
Third-line and plus therapy	Exemestane 25 mg/day	16	26	15	39	–	5	–	–
		19	13	9	30	–	2	26	3
		30	7	15	24	3	4	NR	3
	Letrozole 2.5 mg/day	14	22		58	5	5	20	–

[a]Complete plus partial response
[b]Complete plus partial response, plus stable disease for 24 weeks or more
[c]Based on data from a pooled retrospective analysis

Patients failing antiestrogen therapy

Until recently, progestins were considered standard therapy for postmenopausal women with advanced breast cancer who had progressed on tamoxifen [31]. However, the superior tolerability of anti-aromatase agents compared with megestrol acetate is earning them the status of first choice therapy for these patients (Table 2) [4, 5, 8, 15, 17, 26, 30]. Exemestane has demonstrated superior efficacy compared with megestrol acetate in regard to duration of tumor control, time to progression, time to treatment failure, and survival [17]. Interestingly, exemestane exhibits a higher response rate in patients with visceral disease compared with megestrol acetate, anastrozole, or letrozole [28]. A survival advantage with anastrozole over standard treatment has only been seen when two phase III studies were combined [5]. Letrozole has shown a significant benefit over megestrol acetate in terms of response rate, response duration, time to progression, and time to treatment failure. There was a trend toward increased survival that lacked statistical significance [8].

The newer anti-aromatase agents are also associated with fewer and less-severe side effects than megestrol acetate (Table 2) [4, 8, 25, 30]. Megestrol acetate is associated with a higher incidence of weight gain, edema, and thromboembolic events, whereas patients taking nonsteroidal anti-aromatase agents experience a higher rate of gastrointestinal adverse events. Quality of life assessment indicates that exemestane use is associated with a significant improvement in the number of quality of life subscales including physical functioning, role functioning, and global health compared with megestrol acetate [17].

For patients progressing after tamoxifen, the next choice of therapy should be an anti-aromatase agent. The sequence of therapy remains to be fully defined. While the steroidal agents are effective following relapse on the irreversible drugs, the converse is also true. Thus, anastrozole shows evidence of activity in patients who initially responded or stabilized on the steroidal inactivator, formestane [7].

Patients failing multiple hormonal therapies

The choice of therapy for patients progressing after second-line therapy will ultimately depend on the type and class of hormonal agents used previously. The anti-aromatase agents have demonstrated efficacy in patients progressing after multiple therapies (Table 2). Letrozole has shown efficacy in patients having failed two prior hormonal therapies [14]. Exemestane has demonstrated efficacy in postmenopausal patients refractory to tamoxifen and megestrol acetate [16], tamoxifen and aminoglutethimide [30], and after failure of newer nonsteroidal anti-aromatase agents [19]. The efficacy of formestane (the prototype irreversible aromatase inactivator) in patients failing aminoglutethimide can be explained by its ability to further suppress estrogen levels [22]. Anastrozole has shown evidence of activity in patients who responded or relapsed on formestane.

Although enhanced aromatase inhibition and estrogen suppression could explain the response noted with exemestane following aminoglutethimide treatment, it does not explain the effectiveness of this agent in patients progressing on the newer nonsteroidal anti-aromatase agents. Exemestane was associated with an overall success rate of 13% to 31% in patients treated with anastrozole, letrozole, or vorozole as second- or third-line therapy [19]. Regardless of the mechanism, the lack of cross-resistance observed between exemestane and the nonsteroidal anti-aromatase agents (and vice versa) may be of important clinical significance. In the past, patients failing multiple endocrine therapies were switched to cytotoxic chemotherapy. Considering the limited benefit of second- and third-line chemotherapy in these patients, the ability to continue a patient on hormonal therapy will certainly impact quality of life and, possibly, survival.

The choice of therapy for patients failing multiple hormonal therapies will ultimately be based on prior treatment. Anti-aromatase therapy should definitely be the next therapy in patients progressing on tamoxifen and megestrol acetate. Third-line hormone therapy is reasonable for patients who had achieved a prior response to hormone therapy as up to 25% of these patients have a response to therapy with anti-aromatase agents [22]. For patients who had received prior tamoxifen and anti-aromatase therapy, the use of megestrol acetate as either third- or fourth-line therapy may provide benefit. If the patient has not had prior hormonal therapy, current clinical evidence supports a treatment regimen consisting of either sequential tamoxifen, a nonsteroidal anti-aromatase agent, exemestane and megestrol acetate or sequential tamoxifen, exemestane and megestrol acetate. At this stage, the role of aminoglutethimide is unclear. It is a complex drug associated with significant toxicities. However, if aminoglutethimide was shown to be efficacious in patients failing the newer anti-aromatase agents, it may still be a useful therapy in some cases.

Conclusions

The treatment of advanced postmenopausal breast cancer encompasses a variety of therapeutic options. For the past 40 years, antiestrogens and progestins have served as the foundation of the hormonal armamentarium. Newer more selective approaches are challenging those standards. Estrogen deprivation through inhibition of the enzyme aromatase has proven to be an effective alternate treatment strategy. Based on their enhanced efficacy and favorable tolerability, anti-aromatase agents are emerging as the treatment of choice for patients progressing after tamoxifen therapy and, as use of tamoxifen in the adjuvant setting increases, may

assume a role in the first-line therapy of metastatic disease. Anti-aromatase agents are also being assessed in the adjuvant setting. The results of these trials will help to establish the place of these agents in the treatment of early breast cancer. The broad-based efficacy and good tolerability of the anti-aromatase agents has made them a significant addition to the fight against breast cancer.

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