sensitive to further endocrine therapy

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Summary

Purpose. This retrospective evaluation of data from two randomized, multicenter trials examined whether tumor responses to further endocrine therapy were seen in postmenopausal women with advanced breast cancer who had progressed on both initial endocrine therapy, usually tamoxifen, and on the estrogen receptor (ER) antagonist fulvestrant ('Faslodex').

Patients and methods. A combined total of 423 patients received fulvestrant 250 mg as a monthly intramuscular injection. After progression on fulvestrant, some patients received another endocrine therapy. Responses to subsequent endocrine therapy were assessed using a questionnaire sent to the trial investigators. Best responses were classified as a complete or partial response (CR or PR), stable disease (SD) lasting ≥24 weeks, or disease progression.

Results. Follow-up data were available for 54 patients who derived clinical benefit (CB, defined as CR, PR or SD) from fulvestrant and who received subsequent endocrine therapy, resulting in a PR in 4 patients, SD in 21 patients, and disease progression in 29 patients. Data were available for 51 patients who derived no CB from fulvestrant and who received further endocrine therapy, resulting in a PR in 1 patient, SD in 17 patients, and disease progression in 33 patients. Aromatase inhibitors were used as subsequent endocrine therapy in >80% of patients.

Conclusions. After progression on fulvestrant, patients may retain sensitivity to other endocrine agents. Fulvestrant provides an additional option to existing endocrine therapies for the treatment of advanced or metastatic breast cancer in postmenopausal women, and may provide the opportunity to extend the sequence of endocrine regimens before cytotoxic chemotherapy is required.

Introduction

Despite advances in detection and treatment leading to improved survival, breast cancer represents a leading form of cancer-related death in women. In Europe, breast cancer was the major cause of cancer-related death, leading to approximately 17% of all deaths in 1995 [1]. For hormone-sensitive breast cancers, endocrine therapy is established as the treatment of choice. The selective estrogen receptor modulator (SERM) tamoxifen has for many years been the preferred initial treatment for hormone-sensitive, advanced breast cancer, but aromatase inhibitors (AIs) such as anastrozole and letrozole have been shown recently to be at least as effective [2, 3]. These therapies lead to tumor regression in 40–50% of estrogen receptor (ER)-positive patients [2, 3].

Despite an initial response to tamoxifen, all patients eventually undergo disease progression, necessitating the use of a different therapy. Patients

5]. This sequential use of endocrine therapies offers significant quality-of-life advantages over cytotoxic chemotherapy [4], particularly in elderly patients or those patients with advanced disease, since they offer disease control without the marked adverse events associated with cytotoxic chemotherapy. This sequential use of endocrine agents relies on them possessing different mechanisms of action to overcome cross-resistance, as seen between different SERMs [6]. As a result, the development of novel agents may extend the period of time during which endocrine therapy can be used, thereby deferring the decision to use chemotherapy.

Fulvestrant ('Faslodex') is a new type of antiestrogen, an ER antagonist that dramatically reduces cellular levels of the ER and, importantly, does not possess the partial agonist activity associated with tamoxifen [7, 8]. In preclinical studies, fulvestrant was effective at inhibiting the growth of breast cancer models, both *in vitro* and *in vivo*, including in models of tamoxifen resistance [9, 10]. Phases I and II clinical studies in postmenopausal women with advanced breast cancer who progressed on tamoxifen have demonstrated the efficacy of fulvestrant, with approximately 13/19 (69%) patients showing clinical benefit (CB), without the adverse events associated with tamoxifen (such as hot flashes and night sweats) [11, 12].

Two multicenter phase III trials, prospectively designed to allow the analysis of combined data, compared fulvestrant with anastrozole in postmenopausal women with advanced breast cancer [13, 14]. Fulvestrant was at least as effective as anastrozole and was well tolerated. The work presented here represents the retrospective analysis of combined data from these trials, to evaluate the effects of further endocrine therapies in patients whose tumors became resistant to fulvestrant.

Patients and methods

Trial 0020 was an open, randomized trial conducted in Europe, Australia and South Africa. Trial 0021 was a double-blind, double-dummy, randomized trial conducted in North America. Detailed methodology and results have been previously reported elsewhere [13, 14]. Both trials were conducted with approval from the relevant ethics committees, and all patients gave written, informed consent.

Patients recruited to trials 0020 and 0021 were postmenopausal women with locally advanced or metastatic breast cancer not amenable to curative treatment who had progressed following prior endocrine therapy for advanced or early disease. Patients had histologically or cytologically confirmed breast cancer, with objective evidence of disease recurrence or progression, and at least one measurable lesion. In addition, all patients demonstrated evidence of hormone sensitivity (either sensitivity to $\geq$1 prior hormonal treatment or known ER, or progesterone receptor positivity), a life expectancy of $\geq$3 months, and a WHO performance status of $\leq$2.

Treatment

Patients received fulvestrant 250 mg once monthly and continued treatment until evidence of disease progression or any other significant events warranting withdrawal (e.g., unacceptable adverse events, protocol non-compliance, or withdrawal of patient consent). After this point, treatment ceased and patients undertook standard therapy as determined by their individual clinician. Unless consent was withdrawn, patients were monitored after withdrawal for progression and survival until death.

Data collection

A questionnaire was sent to the trial investigators caring for the fulvestrant-treated patients. Information requested included details of the response to fulvestrant during the trial, details of any subsequent endocrine therapy given after progression, and the best response to this therapy. The efficacy of subsequent endocrine therapy was determined from the investigators responses to the questionnaires. In practice, the treatments used were AIs or megestrol acetate, with some patients receiving medroxyprogesterone acetate.

Results

Of the 423 patients who received fulvestrant in trials 0020 and 0021, 186 derived CB, defined as complete response (CR), partial response (PR), or stable disease (SD) for $\geq$24 weeks, according to UICC criteria. Of these, retrospective follow-up data were available for 66 patients who demonstrated CB on fulvestrant and

	Number of patients	
	Who derived CB from fulvestrant ($n = 54$)	Who did not derive CB from fulvestrant ($n = 51$)
Median age (range), years	61.5 (41–81)	66.0 (42–85)
Site of disease (%)[a]		
Breast	2 (3.7)	6 (11.8)
Skin	8 (14.8)	10 (19.6)
Bone	28 (51.8)	26 (50.9)
Liver	7 (12.9)	15 (29.4)
Lung	19 (35.2)	12 (23.5)
Lymph node	16 (29.6)	17 (33.3)
Other	4 (7.4)	8 (15.7)

[a]Patients may be counted in more than one category.

Table 2. Response to subsequent endocrine therapy in patients who derived CB from fulvestrant (combined data from trials 0020 and 0021)

	Number of patients			
	PR	SD ≥24 weeks	Progression	Total
Endocrine therapy total	4	21	29	54
AIs	3	16	27	46
Anastrozole	1	13	23	37
Letrozole	2	3	3	8
Formestane	0	0	1	1
Megestrol acetate	1	5	2	8

for 84 who did not achieve CB. Further endocrine therapy was received by 54 patients who achieved CB on fulvestrant and by 51 patients who did not achieve CB on trial therapy. These patients were generally well matched in terms of age and site of disease at baseline (Table 1).

The majority of the patients who achieved CB on fulvestrant (46/54; 85%) (Table 2) subsequently received an AI, either anastrozole ($n = 37$), letrozole ($n = 8$) or formestane ($n = 1$), with the remaining patients (15%) receiving megestrol acetate ($n = 8$). Overall, subsequent endocrine therapy in this subset of patients resulted in an objective response (OR) in 4/54 patients and CB in 25/54 patients.

Eighty-two percent (42/51) of the patients who did not derive CB from fulvestrant received an AI as third-line therapy (Table 3): anastrozole ($n = 34$) or letrozole ($n = 8$). The remaining patients (18%) were treated with either megestrol acetate ($n = 6$) or medroxyprogesterone acetate ($n = 3$). The proportion of patients gaining an OR or CB in response to endocrine therapy was lower (1/51 and 18/51, respectively), compared with patients who gained an initial CB from fulvestrant.

A preliminary analysis of the duration of response data (defined as being from the start of treatment through to the date of progression; DoR) showed that the median DoR for patients ($n = 24$) who had CB with fulvestrant was 383 days. For patients ($n = 18$) who did not derive CB on fulvestrant, the DoR on subsequent endocrine therapy was 318 days. Further assessment of endocrine agents subsequent to fulvestrant

	Number of patients			
	PR	SD ≥24 weeks	Progression	Total
Endocrine therapy total	1	17	33	51
AIs	1	15	26	42
Anastrozole	1	11	22	34
Letrozole	0	4	4	8
Megestrol acetate	0	1	5	6
Medroxyprogesterone acetate	0	1	2	3

was not performed, due to an imbalance between the numbers of patients treated with each agent.

Discussion

Extending the period during which endocrine therapy may be used as an effective and viable treatment option for advanced or metastatic breast cancer in postmenopausal women is an important goal. No curative treatment is currently available for many of these patients, and the ability of endocrine therapy to induce responses without producing debilitating toxicities is very valuable. Indeed, many patients are able to derive months, or even years, of high-quality life using sequential endocrine treatment [4]. This sequential use depends on the availability of endocrine agents with differential mechanisms of action, thus avoiding problems of cross-resistance between the various therapies.

This report represents the first examination of sequential endocrine therapy incorporating the ER antagonist fulvestrant before AIs. The results demonstrate that after sequential treatment with tamoxifen and fulvestrant, many patients retain sensitivity to further endocrine therapy with third-generation AIs such as anastrozole and letrozole, or progestins such as megestrol acetate. The rates of CB reported here with endocrine therapy after fulvestrant are similar to those reported for therapy with other endocrine agents (30–50%) [15–17]. Similarly, the CB rates obtained after third-line use of AIs reported here are comparable with previous studies [18]. This indicates that there appears to be incomplete cross-resistance between the different endocrine therapies examined.

The data in this report are limited by the retrospective nature of their collection and the lack of randomization inherent in the use of a questionnaire. Nevertheless, within the limitations imposed by the method used here, responsiveness to fulvestrant appears to be associated with a slightly higher response to subsequent endocrine therapy, compared with those patients who failed to show CB on fulvestrant. Many of these observed responses were SD. The clinical relevance of SD has been demonstrated in a study which showed that patients whose disease stabilized for more than 24 weeks after receiving endocrine therapy, exhibited similar survival to patients who achieved an OR [19]. In addition, patients with an SD response to initial endocrine therapy appear to respond to treatment with subsequent endocrine agents equally as well as patients who derive a CR or PR to initial therapy [20]. Importantly, this suggests that despite the development of resistance, a response to one endocrine agent may predict a response to subsequent agents [20, 21]. Thus, only after failure of multiple prior endocrine therapies would patients be candidates for chemotherapy.

Following progression on tamoxifen, fulvestrant provides an effective treatment option in addition to the currently available endocrine therapies for advanced breast cancer. Progression following treatment with an SERM, and subsequent treatment with an antiestrogen with pure antagonistic properties, does not appear to lead to complete cross-resistance with AIs. Fulvestrant may therefore extend the opportunity for the use of endocrine therapies before reliance on cytotoxic chemotherapy is necessary. In future studies it will be important to examine the activity of fulvestrant after disease progression on AIs, and initial results

with AIs [22]. Data from this and similar trials will be important in further establishing the positioning of fulvestrant in the endocrine sequence for the treatment of advanced breast cancer.

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