Sensitivity to further endocrine therapy is retained following progression on first-line fulvestrant

J.F.R. Robertson[1], A. Howell[2], V.A. Gorbunova[3], T. Watanabe[4], T. Pienkowski[5], and M.R. Lichinitser[3]

[1]*City Hospital, Nottingham, UK;* [2]*Christie Hospital, Manchester, UK;* [3]*Cancer Research Center of Russian Academy of Medical Sciences, Moscow, Russia;* [4]*International University of Health and Welfare, Tochigi, Japan;* [5]*Centrum Onkologii, im M Sklodowskiej-Curie, Warsaw, Poland*

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Summary

There is a need for new endocrine agents that lack cross-resistance with currently available treatments to extend the endocrine treatment window and delay the need for cytotoxic chemotherapy. This retrospective analysis evaluated the response of postmenopausal patients with previously untreated metastatic/locally advanced breast cancer to further endocrine treatment following progression on first-line fulvestrant or tamoxifen. Patients received fulvestrant 250 mg (intramuscular injection every 28 days) plus matching tamoxifen placebo (once daily), or tamoxifen 20 mg (orally once daily) plus matching fulvestrant placebo (every 28 days) in a double-blind, randomized, phase III trial. Treatment continued until disease progression or withdrawal, when further endocrine therapy was initiated (at the treating physician's discretion). Information regarding subsequent therapies and responses was obtained by follow-up questionnaire. Two-hundred-and-forty-five questionnaires were returned (from 587 patients), 149 of which yielded follow-up data on patients receiving second-line endocrine therapy following fulvestrant ($n = 83$) and tamoxifen ($n = 66$). Second-line therapy produced objective responses (OR) in 6/44 (13.6%) and clinical benefit (CB) in 25/44 (56.8%) patients who had CB with fulvestrant and produced OR in 5/41 (12.2%) patients and CB in 27/41 (65.8%) patients who had CB with first-line tamoxifen. For patients deriving no CB from trial therapy, second-line therapy produced OR in 3/39 (7.7%) and CB in 15/39 (38.5%) patients in the fulvestrant group and OR in 4/25 (16.0%) and CB in 12/25 (48.0%) patients in the tamoxifen group. Results from this questionnaire-based study suggest that postmenopausal women with advanced breast cancer who respond to first-line fulvestrant or tamoxifen retain sensitivity to subsequent endocrine therapy.

Introduction

Tamoxifen, a selective estrogen receptor modulator (SERM), is widely used for the first-line treatment of advanced breast cancer in both postmenopausal and premenopausal women and is well established as adjuvant therapy for early breast cancer [1]. Despite an initial response to tamoxifen, many patients eventually undergo disease progression, necessitating the use of different therapies. Many tumors remain hormone sensitive after progression and may respond to subsequent endocrine treatments providing these agents are not cross-resistant. This ability to respond to multiple lines of endocrine therapy may delay the need for the introduction of cytotoxic chemotherapy in some patients.

Fulvestrant is a new type of estrogen receptor (ER) antagonist that has no agonist effects. It binds, blocks and accelerates degradation of the ER leading to reduced cellular levels and subsequent attenuation of estrogen-dependent gene expression [2,3]. In postmenopausal women with advanced breast cancer who have progressed on prior antiestrogen therapy, fulvestrant was found to be at least as effective as the third-generation, highly selective aromatase inhibitor (AI) anastrozole in terms of time to progression (TTP) and objective response (OR; complete response [CR] + partial response [PR]) [4,5]. In a more recent analysis, fulvestrant was shown to be similar to anastrozole with respect to overall survival in this setting [6].

A recent double-blind, randomized, parallel-group study has compared the efficacy and tolerability of fulvestrant and tamoxifen as first-line treatments for postmenopausal women with advanced breast cancer [7]. In patients treated with fulvestrant versus tamoxifen, the OR rate was found to be 31.6 and 33.9% and the median duration of response was 13.8 and 13.9 months, respectively. Median TTP was 6.8 months in the fulvestrant group and 8.3 months in the tamoxifen group (HR = 1.18; 95% CI = 0.98–1.44; $p = 0.0876$), a non-significant difference. The clinical benefit (CB, CR +

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PR + stable disease [SD] ≥24 weeks) rate was 54.3% with fulvestrant and 62.0% with tamoxifen.

Among patients with ER-positive and/or progesterone receptor (PgR)-positive tumors, prospectively planned statistical analyses revealed a small, non-significant estimated treatment difference in OR in favor of fulvestrant (33.2 versus 31.1%; estimated treatment difference 2.1%; odds ratio = 1.10; 95% CI = 0.74–1.63; $p = 0.64$) [7]. In this known receptor-positive group, which comprised ~78% of all patients in the trial, CB rates were 57.1 and 62.7% for fulvestrant and tamoxifen, respectively [7].

Here we report the findings of a retrospective evaluation of the sensitivity of tumors to further endocrine treatment following progression on first-line fulvestrant or tamoxifen within a phase III clinical trial.

Methods

Objective

To obtain data on the ability of patients with advanced breast cancer, who have been treated with first-line fulvestrant or tamoxifen, to respond to subsequent endocrine therapy. Responses to subsequent therapies were compared between patients who did and did not show CB therapy.

Patients

Patients were postmenopausal women with metastatic or locally advanced breast cancer that was ER and/or PgR-positive or ER/PgR status unknown. Patients had received no prior therapy for advanced disease, although some patients (~23%) had received endocrine therapy in the adjuvant setting (tamoxifen treatment that had ceased ≥12 months prior to trial entry in all cases). Women were considered postmenopausal if they met any of the following criteria: aged ≥60 years; aged ≤45 years with amenorrhea for longer than 12 months and with an intact uterus; follicle-stimulating hormone level within postmenopausal range; having undergone a bilateral oophorectomy. Additional inclusion criteria were: histological or cytological proof of breast cancer; the presence of at least one measurable lesion; objective evidence of disease recurrence or progression not considered amenable to curative treatment; World Health Organization (WHO) performance status of 0, 1 or 2; life expectancy >3 months.

Patients were excluded from the trial if they had life-threatening metastatic or visceral disease, a history of brain or leptomeningeal involvement or symptomatic pulmonary lymphangitic spread. Other exclusion criteria included the following: prior treatment with fulvestrant; previous endocrine therapy for advanced breast cancer; treatment with luteinizing hormone-releasing hormone analogs within the previous 3 months; systemic cytotoxic therapy within the previous 4 weeks.

Treatment

Patients were randomized to receive either fulvestrant 250 mg via a 5 ml intramuscular (i.m.) injection once every 28 ± 3 days plus placebo to match tamoxifen 20 mg orally once daily, or tamoxifen 20 mg orally once daily plus placebo to match fulvestrant 250 mg i.m. (5 ml), once every 28 ± 3 days. Treatment continued until disease progression (PD) or withdrawal, after which point further therapy was initiated at the discretion of the treating physician. Unless consent was withdrawn, patients were followed up for progression and survival until death.

Assessment of response to treatment

The best responses to treatment with fulvestrant or tamoxifen during the trial and to subsequent treatment were assessed according to Union Internationale Contre le Cancer (UICC) criteria. Responses were classified as either: CR (defined as disappearance of all known disease), PR (no evidence of PD and a >50% decrease in the size of all measurable lesions and objective improvement in all evaluable, non-measurable lesions), SD (no evidence of PD without evidence for CR or PR) or PD (>25% increase in size of any measurable lesion, worsening of any existing, non-measurable lesion, or the appearance of a new lesion). The OR rate was defined as the proportion of patients with a CR or PR. CB was defined as the proportion of patients with an OR or SD lasting ≥24 weeks.

Information regarding the subsequent therapy and responses were obtained by follow-up questionnaire, sent to all treating physicians. Figure 1 presents the overall treatment scheme for the study and summarizes the outcomes for patients receiving first-line fulvestrant or tamoxifen treatment.

Results

Patients

In total, 313 patients received first-line fulvestrant and of these, 99 patients (31.6%) experienced an OR and 170 (54.3%) derived CB. Two-hundred-and-seventy-four patients received first-line tamoxifen and, of these, 93 (33.9%) experienced an OR and 170 (62.0%) derived CB. Two-hundred-and-forty-five questionnaires were returned by trial investigators, 149 of which yielded evaluable follow-up data on patients who had received second-line endocrine therapy (83 treated with first-line fulvestrant and 66 treated with first-line tamoxifen). Reasons for follow-up data being unavailable were as follows: patient did not receive second-line endocrine treatment; patient received more than one endocrine therapy as second-line treatment; patient received chemotherapy as second-line treatment; investigator unable to assess response; insufficient patient records; patients

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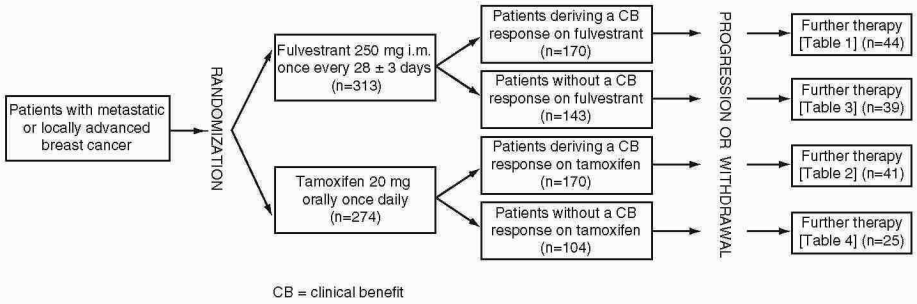

Figure 1. Study treatment scheme and outcomes for patients receiving first-line fulvestrant or tamoxifen.

were lost to follow-up; questionnaires were not returned; patient consent withdrawn in follow-up phase; and second-line endocrine treatment stopped before assessment of response due to side effects.

Response to subsequent endocrine therapy in patients deriving CB from first-line endocrine treatment

Overall, 85 of the 149 (57.0%) patients with available follow-up data derived CB from first-line treatment (44/83 [53.0%] treated with fulvestrant, 41/66 [62.1%] treated with tamoxifen).

CB with first-line fulvestrant

Of the 44 patients who derived CB from first-line fulvestrant and had follow-up data available, second-line treatments included: AIs ($n=29$; anastrozole [$n=20$], letrozole [$n=7$], fadrozole [$n=1$], aminoglutethimide [$n=1$]), tamoxifen ($n=12$), medroxyprogesterone acetate ($n=2$), and megestrol acetate ($n=1$). Second-line hormonal therapy produced an OR in 6/44 (13.6%) and CB in 25/44 (56.8%) patients (Table 1). Nineteen patients (43.2%) did not respond to second-line endocrine therapy.

CB with first-line tamoxifen

Of the 41 patients who had CB with first-line tamoxifen and had follow-up data available, second-line treatments included AIs ($n=31$; anastrozole [$n=21$], letrozole [$n=5$], fadrozole [$n=2$], exemestane [$n=3$]), megestrol acetate ($n=5$), fulvestrant ($n=1$), and medroxyprogesterone acetate ($n=1$). In addition, three patients were administered commercially available tamoxifen as their second-line therapy. Second-line hormonal therapy produced an OR in 5/41 (12.2%) patients and CB in 27/41 (65.8%) patients (Table 2). Fourteen patients (34.1%) did not respond to second-line endocrine therapy. In the three patients who received second-line tamoxifen, a best response of SD was reported in each case.

Response to subsequent endocrine therapy in patients who derived no CB from first-line endocrine treatment

Sixty-four of the 149 (43.0%) patients with available follow-up data did not derive CB from trial therapy (39/83 (47.0%) treated with fulvestrant, 25/66 (37.9%) treated with tamoxifen).

No CB with first-line fulvestrant

Of the 39 patients who did not derive CB from first-line fulvestrant and had follow-up data available, second-line treatments included AIs ($n=22$; anastrozole [$n=12$], letrozole [$n=6$], fadrozole [$n=3$], exemestane [$n=1$]), tamoxifen ($n=12$), megestrol acetate ($n=1$), and medroxyprogesterone acetate ($n=4$). Second-line therapy produced an OR in 3/39 (7.7%) and CB in 15/39 (38.5%) patients (Table 3). Twenty-four (61.5%) patients did not respond to second-line endocrine therapy.

Table 1. Response to subsequent therapy in patients who derived clinical benefit from fulvestrant as trial therapy

	Number of patients					
	Total	CR	PR	SD	CB	PD
Endocrine therapy	44	3	3	19	25	19
Aromatase inhibitors	29	1	2	11	14	15
Anastrozole	20	1	0	10	11	9
Letrozole	7	0	2	0	2	5
Fadrozole	1	0	0	1	1	0
Aminoglutethimide	1	0	0	0	0	1
Tamoxifen	12	2	1	7	10	2
Megestrol acetate	1	0	0	1	1	0
Medroxyprogesterone acetate	2	0	0	0	0	2

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; CB = clinical benefit; PD = disease progression.

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Table 2. Response to subsequent therapy in patients who derived clinical benefit from tamoxifen as trial therapy

	Number of patients					
	Total	CR	PR	SD	CB	PD
Endocrine therapy	41	2	3	22	27	14
Aromatase inhibitors	31	2	3	16	21	10
Anastrozole	21	2	2	10	14	7
Letrozole	5	0	1	3	4	1
Fadrozole	2	0	0	0	0	2
Exemestane	3	0	0	3	3	0
Megestrol acetate	5	0	0	2	2	3
Tamoxifen	3	0	0	3	3	0
Fulvestrant	1	0	0	0	0	1
Medroxyprogesterone acetate	1	0	0	1	1	0

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; CB = clinical benefit; PD = disease progression.

No CB with first-line tamoxifen

Of the 25 patients who did not derive CB from first-line tamoxifen and had follow-up data available, second-line treatments included AIs ($n=17$; anastrozole [$n=10$], letrozole [$n=6$], exemestane [$n=1$]), megestrol acetate ($n=4$) and medroxyprogesterone acetate ($n=2$). Second-line therapy produced an OR in 4/25 (16.0%) and CB in 12/25 (48.0%) patients (Table 4). Thirteen patients (52.0%) did not respond to second-line endocrine therapy. Two patients who progressed on tamoxifen were given commercial tamoxifen as subsequent therapy.

Discussion

These data represent the first evaluation of responses to treatment following first-line fulvestrant in patients with advanced disease previously untreated with endocrine therapy. A total of 245 (42%) questionnaires were returned by trial investigators, which yielded usable follow-up data from 149 (25.4%) of the patients randomized to treatment. Retrospective questionnaire-based analyses such as this may however be open to bias and in the absence of data collected from randomized trials, these results should be considered informative rather than definitive.

Although derived from less than half the eligible patients, these data suggest that more than 50% of patients with follow-up data available who previously derived CB from initial fulvestrant or tamoxifen treatment may retain sensitivity to subsequent endocrine therapy. Of those patients not responding to initial endocrine treatment, a slightly lower proportion (~38–48%) derived CB from subsequent therapy. This latter figure, which is slightly higher than expected for second-line endocrine therapy in patients with tumors that showed *de novo* progression to first-line endocrine therapy, was similar whether the initial therapy had been tamoxifen or fulvestrant.

Second-line treatment with AIs such as anastrozole or letrozole produced similar response rates in patients who had not responded to fulvestrant or tamoxifen. It is of interest to note that following first-line fulvestrant, it appears that more patients received an AI as second-line treatment, compared with tamoxifen. This is consistent with the fact that AIs are now more frequently being prescribed as first-line treatment for postmenopausal patients with advanced breast cancer. However, what is also clear is that after first-line fulvestrant, the CB rate

Table 3. Response to subsequent therapy in patients who did not derive clinical benefit from fulvestrant as trial therapy

	Number of patients					
	Total	CR	PR	SD	CB	PD
Endocrine therapy	39	0	3	12	15	24
Aromatase inhibitors	22	0	0	9	9	13
Anastrozole	12	0	0	7	7	5
Letrozole	6	0	0	2	2	4
Fadrozole	3	0	0	0	0	3
Exemestane	1	0	0	0	0	1
Tamoxifen	12	0	3	2	5	7
Megestrol acetate	1	0	0	1	1	0
Medroxyprogesterone acetate	4	0	0	0	0	4

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; CB = clinical benefit; PD = disease progression.

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Table 4. Response to subsequent therapy in patients who did not derive clinical benefit from tamoxifen as trial therapy

	Number of patients					
	Total	CR	PR	SD	CB	PD
Endocrine therapy	25	0	4	8	12	13
Aromatase inhibitors	17	0	3	7	10	7
Anastrozole	10	0	2	5	7	3
Letrozole	6	0	1	2	3	3
Exemestane	1	0	0	0	0	1
Tamoxifen	2	0	0	0	0	2
Megestrol acetate	4	0	1	1	2	2
Medroxyprogesterone acetate	2	0	0	0	0	2

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; CB = clinical benefit; PD = disease progression.

to second-line tamoxifen (10/12) is at least as good as to an AI (14/29). It should be noted that this is a retrospective questionnaire-based study with data on just under half the patients who were randomized into the study. As such we should interpret these findings with some caution and should not make statistical comparisons between tamoxifen and AIs based on this dataset. It should also be noted that although some patients received tamoxifen as subsequent therapy in this study, no patients received fulvestrant other than the prospective study context of first-line endocrine therapy since, at that time, fulvestrant was not licensed in the EU.

The proportion of post fulvestrant responses reported here is similar to those previously described for second-line AI therapy in patients who failed on first-line tamoxifen treatment [8,9]. For example, in a study by Buzdar et al., CB was observed in 111/263 (42.3%) patients treated with second-line anastrozole [8] and in a study by Kvinnsland et al., CB was noted in 65/137 (47.4%) patients receiving exemestane as second-line treatment [9]. The CB rate for those patients who were known not to have responded to prior tamoxifen was 60% versus 47% for those who did respond [9]. In the present study, CB was observed in 11/20 (55.0%) patients treated with second-line anastrozole after demonstrating CB with first-line fulvestrant treatment and in 7/12 (58.3%) patients treated with second-line anastrozole after not responding to first-line fulvestrant treatment.

Our results are similar to those gained in a recent retrospective analysis of response to subsequent endocrine treatment in 105 patients who had progressed on both initial endocrine therapy, usually tamoxifen, and on second-line fulvestrant. Of the 54 patients included in the analysis and who derived CB from fulvestrant treatment, 25 (46.3%) derived CB from subsequent endocrine treatment. In the group of patients who did not derive CB from fulvestrant treatment ($n = 51$), 18 patients (35.3%) derived CB from subsequent treatment. In this study, AIs were used as subsequent endocrine therapy in >80% of patients [10]. Furthermore, preliminary results have been reported from an ongoing Phase II trial determining the efficacy of fulvestrant in patients with advanced breast cancer who have progressed on prior endocrine therapy with tamoxifen and AIs. Here, CB was reported in 7/17 (41.2%) eligible patients after tamoxifen and AI failure [11]. Additionally, in compassionate use programs, CB has been observed in patients receiving fulvestrant after progression on multiple prior endocrine therapies, including both SERMs and AIs [12–14].

Conclusions

The direct comparison between tamoxifen and fulvestrant as first-line endocrine therapy has been addressed in a previous publication [7]. This manuscript has focused on sequencing and whether the use of one or other of these drugs as first-line therapy makes tumors more likely to become hormone insensitive.

Postmenopausal women with advanced breast cancer who respond to first-line fulvestrant or tamoxifen appear to retain sensitivity to subsequent endocrine therapy, suggesting that subsequent progression after ER downregulation may not be due to loss of hormone sensitivity. In particular, CB rates to either tamoxifen or AIs subsequent to first-line fulvestrant appear similar, although the number of patients in each sub-group is relatively small. When AIs are used second-line, the response rates in patients who have progressed on fulvestrant or on tamoxifen are similar. These findings suggest that in terms of response to subsequent (i.e. second-line) endocrine therapy, there does not appear to be a difference between initial (i.e. first-line) antiestrogen therapy with tamoxifen or fulvestrant. In other words, fulvestrant is no more likely than tamoxifen in induce hormone insensitivity. Therefore, fulvestrant appears to offer an opportunity to prolong the time in which well-tolerated endocrine therapies are used before reliance upon cytotoxic chemotherapy is necessary.

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