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CLINICAL TRIAL

Fulvestrant ('Faslodex') in heavily pretreated postmenopausal patients with advanced breast cancer: single centre clinical experience from the compassionate use programme

Brigitte Mlineritsch · Oskar Psenak · Peter Mayer · Martin Moik · Konrad Namberger · Cornelia Hauser-Kronberger · Richard Greil

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Abstract
Background Fulvestrant (Faslodex) is an oestrogen receptor (ER) antagonist with demonstrated efficacy in patients with advanced and pretreated breast cancer.
Patients and methods We present a single-centre experience with fulvestrant administered under the compassionate use programme (CUP) to a total of 54 postmenopausal women with metastatic breast cancer progressing on multiple endocrine and cytotoxic therapies. Patients received 250 mg fulvestrant i.m. once monthly as second- ($n = 8$), third- ($n = 30$), fourth- ($n = 14$) and fifth-line ($n = 2$) hormonal treatment. The median number of previous endocrine therapies was 2 (range 1–4). Most of the patients also had multiple palliative chemotherapies with a median of 1.7 (range 0–6) prior therapies. The median duration of fulvestrant treatment was 6.3 months (range 1–39 months) and the median duration of follow-up was 19.4 months (range 1–63 months).
Results Objective response was achieved by five patients (9.3%): one complete remission (CR) (1.9%) and four partial remissions (PR) (7.4%). Stable disease (SD) lasting ≥6 months was achieved by 16 patients (29.6%). Thus in all, fulvestrant conferred clinical benefit (CB) on 21 women (38.9%). The median time to progression (TTP) was 6.4 months. In all patients with CR and PR, tumour cells were positive for both ER and progesterone receptor (PgR), but lacked HER2/neu overexpression; one patient with PR had an unknown HER2/neu status. Overall, the drug was well tolerated. No grade 3/4 toxicities were reported.
Conclusions Fulvestrant appears to be an efficient and well-tolerated drug even in women with advanced breast cancer progressing after multiple endocrine and/or cytotoxic treatments.

Keywords Advanced breast cancer · Endocrine resistance · Fulvestrant · Pretreatment regimens

B. Mlineritsch and O. Psenak contributed equally to the work.

B. Mlineritsch · O. Psenak · P. Mayer · M. Moik · K. Namberger · R. Greil (✉)
III Medical Department with Haematology, Medical Oncology, Haemostaseology, Rheumatology and Infectious Disease, Paracelsus Private Medical University Salzburg, and Laboratory of Immunological and Molecular Cancer Research, Müllner Hauptstrasse 48, 5020 Salzburg, Austria
e-mail: r.greil@salk.at

C. Hauser-Kronberger
Department of Pathology, Paracelsus Private Medical University Salzburg, Salzburg, Austria

Introduction

In the endocrine therapeutic armamentarium of hormone-responsive advanced breast cancer, fulvestrant (F) represents a promising therapeutic option. It binds to oestrogen receptor (ER) with an affinity similar to that of oestradiol (E) and dissociates heat shock protein 90 (HSP90) causing a rapid degradation of ER and reduced binding of F-ER to the oestrogen response element (ERE) [1]. Nawaz et al. demonstrated an anti-oestrogenic and antiprogestin activity of fulvestrant [2]. Furthermore, fulvestrant was shown to inhibit invasiveness of breast cancer cells [3].

Two international randomized phase III trials have studied the efficacy of fulvestrant in women with advanced breast cancer who had progressed on a first line endocrine treatment with tamoxifen [4, 5].

However there are only a very few studies with small cohorts on the efficacy of fulvestrant in patients who had progressed on more than one hormonal or cytotoxic treatment.

Under a compassionate use programme (CUP), efficacy and tolerability of fulvestrant were assessed in postmenopausal women with metastatic breast cancer who progressed despite multiple prior endocrine and cytotoxic therapies. Additionally, quality of life (QOL) of these patients was evaluated. We found that clinical benefit (CB) was achieved by a number of these patients, indicating the value of this drug even in this highly pretreated group. According to our knowledge, the present study is one of a small number of reports assessing the efficacy of the drug in a cohort of patients with the largest number of pretreatments.

Patients and methods

The CUP was carried out between 5 May 2000 and 1 July 2005. All data were collected from the III Medical Department with Haematology, Medical Oncology, Haemostaseology, Rheumatology and Infectious Disease at the Paracelsus Private Medical University Salzburg, Austria.

Patients' characteristics

The CUP programme covered 54 postmenopausal women aged 42–81 years (median of 60 years) with histologically confirmed, hormone receptor-positive, locally advanced or metastatic breast cancer with progression, as determined by the criteria of the WHO classification, on one or more endocrine and cytotoxic treatments.

Patients fulfilling the following criteria were excluded: presence of life-threatening metastatic disease, lymphoedema as the only breast cancer-related lesion, patients who had Faslodex or systemic cytotoxic or radiation therapy in the immediately preceding 4 weeks, previous or current systemic malignancy other than breast cancer within the last 3 years (except adequately treated in-situ carcinoma of the cervix uteri, or basal or squamous cell carcinoma of the skin), patients currently receiving oestrogen replacement therapy, those with platelet counts less than 100×10^9/l, total bilirubin >1.5 times the upper limits of the reference range (ULRR), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 times the ULRR (or >5 times the ULRR in the presence of liver metastases), with International Normalized Ratio (INR) >1.6, with a history of bleeding diathesis or a history of hypersensitivity to Faslodex.

All subjects had a positive receptor status, 48 of them (88.9%) were positive for both ER and progesterone receptor (PgR); epidermal growth factor receptor 2/neu (HER2/neu) status was negative in 28 (51.9%), positive in 8 (14.8%) and unknown in 18 (33.3%) patients (for patient characteristics see Table 1).

The receptor status and metastatic sites are shown in Table 1 and Fig. 1, respectively.

Hormone receptor and HER2/neu status

Hormone receptor status (ER and PgR) was assessed using immunohistochemistry, with tumour expression being classified as either positive (ER-positive and/or PgR-positive) or negative (ER- and PgR-negative) according to the classification system of McGuire et al. [6] HER2/neu status was assessed using the Herceptest® (Dako A/S, Glostrup, Denmark) or dual colour fluorescent in situ hybridization (FISH; PathVision® DNA probe kit, Vysis Inc., Downers Grove, IL, USA). Tumours were classed as HER2/neu-positive if they had a staining intensity of +++ on the Herceptest; if the score was ++, the tumours were reanalysed using FISH [7]. Results of HER2/neu assessment are given in Table 1.

Pretreatment regimens

The previous adjuvant treatment regimens are listed in Table 2. The numbers and types of previous endocrine and cytotoxic treatment regimens applied in the palliative setting prior to inclusion in the fulvestrant programme are given in Tables 3 and 4. All patients had undergone antihormonal treatment and 81.5% had

Table 1 Receptor characteristics

Patient characteristic	*n*	%
Total number of patients	54	100
Median age, years (range)	60 (43–81)	
Disease-free interval, years (range)	6 (0–21)	
ER + PgR+	48	88.9
ER + PgR-	5	9.3
ER - PgR+	1	1.9
ER - PgR-	0	0
HER2/neu+	8	14.8
HER2/neu-	28	51.9
HER2/neu unknown	18	33.3

ER oestrogen receptor, *PgR* progesterone receptor, *HER2/neu* human epidermal growth factor receptor 2

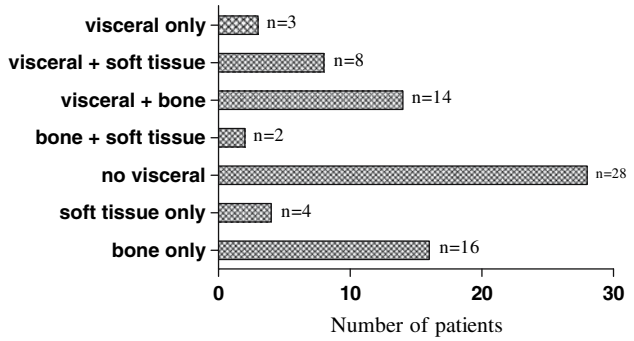

Fig. 1 Distribution of metastatic sites. Absolute numbers are given. Each individual site was counted separately in this analysis

Table 2 Drugs used prior to fulvestrant treatment in the adjuvant setting

Adjuvant pretreatment	*n*	%
Cytotoxic only	10	18.5
Endocrine only	19	35.2
Cytotoxic and endocrine therapies	7	13.0
No adjuvant therapy	14	25.9
Unknown	4	7.4

Table 3 Number and types of palliative endocrine treatment regimens prior to the inclusion in the fulvestrant programme

Palliative endocrine therapy	*n*	%
Tamoxifen	31	57.4
Anastrozole	37	68.5
Exemestane	27	50.0
Letrozole	10	18.5
Goserelin	6	11.1
Medroxyprogesterone acetate	6	11.1
4-hydroxyandrostenedione	1	1.9
Fulvestrant by line of endocrine therapies		
Second line	8	14.8
Third line	30	55.6
Fourth line	14	25.9
Fifth line	2	3.7
Mean number of palliative endocrine therapies	2	Range 1–4

also additionally received chemotherapy. The mean number of both cytotoxic and endocrine therapies was 3.7 (range 1–9). The distribution of chemotherapy regimens was as follows: 25 patients had previously received anthracyclines either alone or in combination (i.e. caelyx 8 (14.8%), mitoxantrone 6 (11.1%), caelyx + vinorelbine 1 (1.9%), EC (cyclophosphamide and epirubicin) 10 (18.5%), anthracyclines + taxanes 2 (3.7%)); 25 patients had received 5-FU-based regimens (capecitabine 5 (9.3%), CMF (cyclophosphamide, methotrexate and 5-FU) 10 (18.5%) or vinorelbine, 5-FU and LV (leucovorin) 10 (18.5%)). Eight patients

Table 4 Number of chemotherapy regimens in the palliative setting prior to treatment with fulvestrant

Number of palliative chemotherapy regimens	*n*	%
0	10	18.5
1	15	27.8
2	13	24.1
3	9	16.7
4	4	7.4
6	1	1.9
Unknown	2	3.7
Mean number of palliative chemotherapy regimens	1.7	Range 0–6

(14.8%) had received taxanes without anthracyclines and 11 (20.4%) of patients were pretreated with gemcitabine ± vinorelbine. Trastuzumab was preferentially applied together with taxanes (1) or vinorelbine (3). Other regimens were applied in nine patients and ten received no cytotoxic therapy.

All patients provided written informed consent. Fulvestrant (Faslodex®) was purchased using the ''Named Patient Request Form'' from Astra Zeneca (Wien, Austria, EU) and administered at a dose of 250 mg i.m. every 4 weeks until objective disease progression or other events that required discontinuation of treatment.

Response assessments

Response to treatment was assessed every 3 months using World Health Organisation (WHO) response criteria [8]. As this was a single centre prescribing fulvestrant as part of a CUP and not a controlled clinical trial, there was no external review of response rates. Complete response (CR) was defined as the radiological disappearance of all measurable disease, partial remission (PR) was defined as a ≥50% decrease in tumour size or in the sum of all measurable lesions, and stable disease (SD) was defined as a <50% decrease or a <25% increase in tumour size without the appearance of new lesions. Progressive disease (PD) was defined as a ≥25% increase in tumour size or the appearance of new lesions.

Time to progression (TTP) was defined as the time from the start of fulvestrant administration until objective disease progression or death from any cause. CB was defined as the sum of complete and partial response and SD lasting ≥24 weeks. Overall survival (OS) was calculated as the period from the first dose of fulvestrant to the date of death. Data from TTP and OS were summarized in the Kaplan–Meier curves.

Tolerability

Adverse events during fulvestrant treatment were recorded and graded according to the National Cancer Institute Common Toxicity Criteria [9].

Quality of life

Quality of life was monitored using a QLQ-C30 questionnaire comprising 30 questions concerning the functional and physical fitness of the patients [10]. Questionnaires were evaluated at the time of inclusion and at intervals of 2–3 months during the course of treatment with fulvestrant, till disease progression was established. Global QOL score of the patients was assessed. The significance of longitudinal changes in QOL was tested by the Student's *t*-test.

Results

Response to treatment

All patients were available for evaluation of response. The median duration of fulvestrant treatment was 6.3 months (range 1–39 months) and the median duration of follow-up was 19.4 months (range 1–63 months). One patient reached complete remission (1.9%), four patients PR (7.4%), 26 patients (48.1%) experienced SD, with 16 (29.6%) of them having SD for a period longer than 24 weeks after fulvestrant therapy. Thus, CB was observed in 21 women (38.9%). Primary progressive disease was found in 23 women (42.6%). At the time of data cut-off, 38 patients (70.4%) had died because of disease progression. The median TTP was 6.4 months (range 0.7–39.6 months), the median OS was 19.4 months (range 1–62.8) (Fig. 2).

Response according to receptor status

Clinical benefit was achieved in a similar proportion of patients with tumour cells positive for both ER and PgR as well as in those staining only for ER, whereas objective tumour regression was exclusively observed in double-positive patients (Table 5). The number of patients with ER-/PgR+ disease is too small to allow any conclusion, but the single patient included in this group experienced SD ≥24 weeks.

The HER2/neu status was known in 36 women (66.7%, Table 1). CR and PR were only observed in HER2/neu-negative patients. However, the CB ratio achieved with fulvestrant was comparable between patients with HER2/neu-positive and HER2/neu-negative status (Table 6).

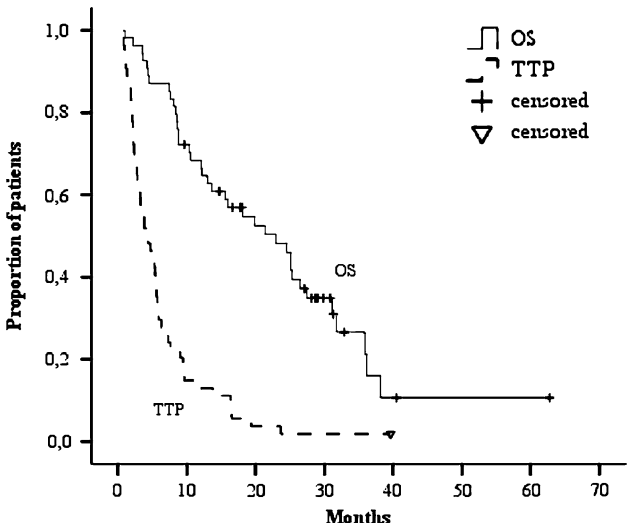

Fig. 2 Kaplan–Meier curve estimates for time to progression (*TTP*) and overall survival (*OS*) in months

Response according to metastatic sites

Three of four patients (75%) with exclusively soft tissue metastases derived CB from treatment with fulvestrant, one achieving CR (25%), one PR (25%) and one SD ≥24 weeks. Four of 16 women (25%) with only bone metastases experienced CB (two of them achieving PR, 12.5%). All the three patients who had only visceral metastases experienced PD (Fig. 3).

Response according to endocrine and cytotoxic pretreatments

The patient with CR received fulvestrant as second-line treatment. Two of four patients who achieved PR received fulvestrant as third-line and two as fourth-line of palliative endocrine treatment while two other patients reached SD under fifth-line treatment with this drug. Thus it can be seen that fulvestrant conferred CB even on patients with a large number of prior endocrine treatments (Fig. 4).

Women with no, one, two, three and four chemotherapy pretreatments achieved CB in 50, 33, 35.7, 55.6 and 33% of cases, respectively. One patient in each group pretreated with one, two and three lines of chemotherapy reached PR (6.7, 7.1 and 11.1%, respectively) (Fig. 5).

All women who derived CR or PR on fulvestrant had tumours positive for both ER and PgR, and with the exception of one patient all had a negative HER2/

Table 5 Response to fulvestrant according to the HR status

Hormone receptor status	Total number	CR	PR	SD	CB	PD
ER + PgR+	48	1 (2.1%)	4 (8.3%)	22 (45.8%)	17 (35.4%)	21 (43.8%)
ER + PgR-	5	–	–	3 (60%)	2 (40%)	2 (40%)
ER – PgR+	1	–	–	–	1	–

Table 6 Response to fulvestrant according to the HER2/neu status

HER2/neu status	Total	CR	PR	SD	CB	PD
HER2/neu+	8	–	–	5 (62.5%)	4 (50%)	3 (37.5%)
HER2/neu-	28	1 (3.6%)	3 (10.7%)	11 (39.3%)	10 (35.7%)	13 (46.4%)

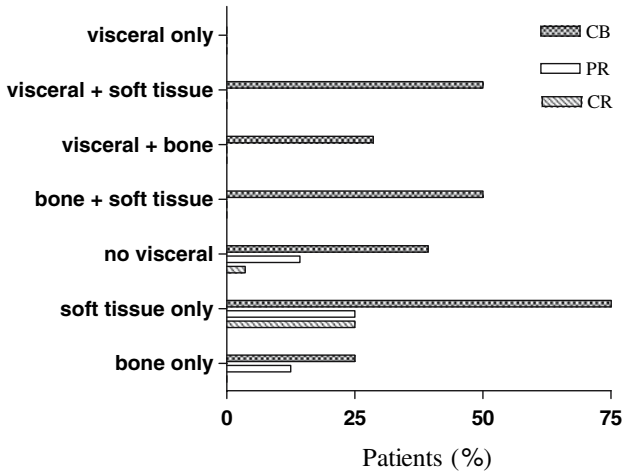

Fig. 3 Response to fulvestrant according to metastatic sites

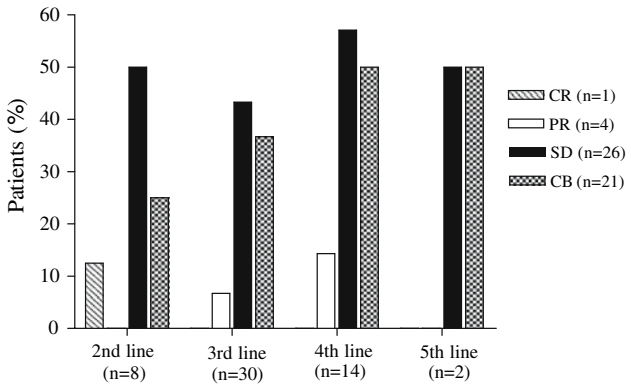

Fig. 4 Response to fulvestrant after multiple palliative antihormonal lines. Columns are related to fulvestrant administration as 2nd, 3rd, 4th and 5th line of endocrine therapy

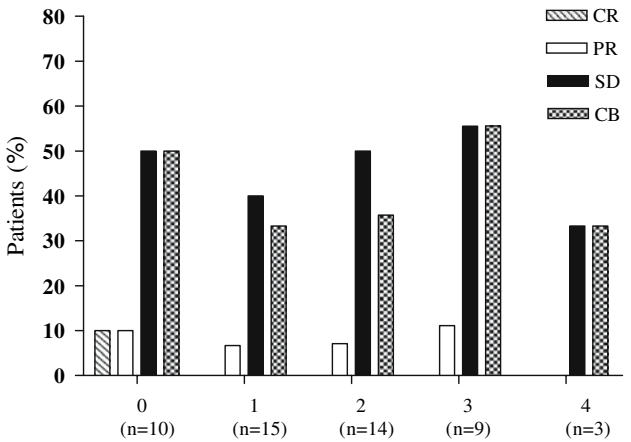

Fig. 5 Response to fulvestrant after multiple palliative chemotherapy regimens: Columns are related to 0–4 lines of cytotoxic pretreatment

neu status. All had multiple palliative cytotoxic and endocrine regimens (the patient with CR had received only tamoxifen). None of them had visceral metastases.

Tolerability

During fulvestrant treatment, adverse effects were reported by 24 patients (44.4%). All events were grade 1 or 2. Nausea and asthenia were the most common reported toxicities (Table 7). Although fulvestrant has not raised safety concerns so far, it should be mentioned that adverse-event reporting in CUPs is not as rigorous as in a controlled clinical trial setting.

Quality of life

Tolerability of the investigated drug was evaluated using QLQ-C30 questionnaire and median values ± SEM were compared: once, at the time of inclusion in the programme and again at intervals of 1–3 months, unless the patient was progressive earlier. Only 19 women filled in two questionnaires. Differences in the willingness of patients to complete questionnaires are a well-known phenomenon in patients

Table 7 Side effects of fulvestrant therapy

Adverse effects	*n*	%
Nausea	13	24.1
Asthenia	10	18.5
Vomiting	5	9.3
Anorexia	2	3.7
Dizziness	2	3.7
Dyspnoea	2	3.7
Flushing	2	3.7
Constipation	1	1.9
Depression	1	1.9
Diarrhoea	1	1.9
Insomnia	1	1.9
Vaginal bleeding	1	1.9

Only grade 1, 2 side effects were observed

with metastatic disease and this willingness is known to decrease in the longitudinal run [11, 12]. First, we compared the QOL in women who experienced CB. Patients retained their mental and physical fitness over time. Then, we compared the QOL between patients who derived CB and who were primarily progressive on fulvestrant. Women who developed progressive disease did not show significant deterioration in their QOL over subsequent analyses. Overall, there was no significant change in patients' mental and physical status apart from their response to treatment.

Discussion

Patients with metastatic breast cancer have improved prognosis [13, 14], particularly those with hormone-responsive disease [13] due to the availability of an increasing number as well as new classes of drugs such as aromatase inhibitors, which demonstrate a survival benefit over tamoxifen when used as 1st line treatment of HR-positive patients [15]. Our study showing CB of fulvestrant in several subjects with multiple prior endocrine and cytotoxic treatments suggests the possibility of maintaining patients on antihormonal treatment who otherwise would have to be changed to cytostatic therapy because of disease progression under endocrine therapy or of changing back to endocrine therapy after previous failed cytotoxic therapy. Little, however, is known concerning the proper sequence of fulvestrant within antihormonal or sequential cytotoxic and antihormonal regimens. With metastatic breast cancer becoming more and more a chronic disease, optimization of antihormonal sequences may help prevent or delay development of cross-resistance and offer well tolerable treatment options. In addition, efficacy in the metastatic setting might encourage clinical trials investigating the potential benefit of fulvestrant in neoadjuvant or adjuvant treatment strategies.

The observed response rate of 9.3% (CR + PR) and CB ratio of 38.9% (CR + PR + SD ≥24 weeks) in women with a median number of three prior therapy regimens does not markedly differ from the CUP reports of Steger et al. [16] and those of Osborne et al. [4] and Howell et al. [5], despite the fact that the latter authors had included only patients in a much earlier phase of the disease, i.e. after prior adjuvant or 1st line palliative endocrine therapy. While this result may reflect a positive selection bias of prognostically favourable, continuously hormone-sensitive patients, it draws attention to the late occurrence of cross-resistance to other drugs. This point is also supported by Steger et al. who demonstrated that CB under fulvestrant remained unchanged with increasing number of prior antihormonal treatment, although response rates decreased with an increasing line in endocrine treatment sequence [16]. Fulvestrant has been reported to be effective in women with prior treatment with aromatase inhibitors alone (52.4% CB) compared with women whose prior treatment also included tamoxifen (28.6% CB) [17]. In our study, the mean TTP was 6.3 months—a time period slightly longer than that reported in other trials mentioned above—which supports the usefulness of fulvestrant treatment even in a subset of patients with a significantly larger number of prior therapy regimens, provided they did not display visceral metastases (Figs. 4, 5).

Of 54 women included in our study, one reached CR (1.9%) and four developed PR (7.4%). Two of them who achieved PR were older than 70 years of age and received fulvestrant as third- or fourth-line endocrine therapy. Their receptor status and preferential metastatic sites suggest criteria for selecting patients for treatment with fulvestrant: ER+, PgR+, HER2/neu-, non-visceral metastases and established hormone responsiveness. In fact, the highest degree of tumour regression was seen in ER+/PgR+ patients who were the only patients to achieve a PR.

All our patients with CR and PR were HER2/neu-negative except one with unknown HER2/neu receptor status, which is in agreement with the predicted association of HER2/neu-positive disease with endocrine resistance in general or at least with a lower rate of responsiveness (18). Notably, however, CB was achieved by 50% of HER2/neu-positive patients. It is clear that more studies are needed to determine the efficacy of fulvestrant in relation to HER2/neu status of advanced metastatic breast cancer.

Only few PRs were achieved under fulvestrant, with most of CB representing disease stabilization.

Therefore, the drug is not suitable for rapid tumour mass reduction, particularly in primarily visceral types of metastatic spread. The median time to onset of response in our patients was 3.9 months (range 2.9–5.5 months).

Response to the drug was different in patients with different localization of metastases, but with the number of women in each group being small, no firm conclusions can be drawn. The best response was observed in patients with only soft tissue metastases; 75% achieved CB including the one patient who gained complete remission. The best response reported so far was in patients with bone metastases [16]. We did not see CB in women with only visceral metastases, which is in striking contrast to the report of Steger et al. [20].

Fulvestrant is a well-tolerated drug since patients reported only grade 1/2 adverse effects, nausea and fatigue being predominant among them. These observations are concordant with data presented by Osborne et al. [4], Howell et al. [5] and Steger et al. [16].

In addition, QOL did not decrease over the treatment period, which correlates with published data [4, 5]. This might be due to the fact that most of these patients were largely asymptomatic at the time of diagnosis, and disease progression was slow. However, it must be pointed out that no significant difference between those who had CB and those who progressed on fulvestrant was observed.

Conclusion

Data from CUP and other investigations confirm the potential of fulvestrant to stop progression of metastatic, hormone-sensitive breast cancer and to confer CB on a sizeable proportion of patients progressing on multiple lines of endocrine or cytotoxic treatments. Although it cannot be excluded that these patients represent a cohort of those with biologically and histologically favourable hormone responsive cancers, efficacy of the drug in these patients warrants its testing in clinical trials as neoadjuvant and postoperative treatment. Studies in which therapy was switched from tamoxifen to an aromatase inhibitor after different time periods report prolongation of TTP to metastatic disease [21, 22] and even of OS [22]. In addition, emerging data suggest that the sequence of antihormonal drugs may influence the time to development of resistance [23]. A more detailed analysis of sequential treatments in the CUP will help define the role of fulvestrant in early breast cancer. In the meantime, current evidence of some efficacy in heavily pretreated patients gives hope that further investigations might demonstrate the therapeutic potential of fulvestrant earlier in the course of the disease.

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