Fulvestrant: A Further Treatment Option for Patients with Metastatic Uterine Cancer?

Michael P. Lux^a Evelyn M. Wenkel^b Kai Beckmann^a Matthias W. Beckmann^a Falk Thiel^a

^aDepartment of Obstetrics and Gynecology,

^bInstitute of Radiology, Universitätsklinikum Erlangen, Germany

Key Words

Uterine cancer, advanced · Fulvestrant · Endocrine therapy · Hepatic metastases

Summary

Background: Metastatic uterine cancer is notoriously difficult to treat, presenting a poor prognosis and a median survival time of less than 1 year. We present the successful use of the antiestrogen fulvestrant in an endocrine therapy-naïve patient with advanced uterine cancer. **Case Report:** A 64-year-old female presented with advanced uterine cancer 7.0 × 6.0 × 5.5 cm in size, with infiltration of the bladder. Previous chemotherapy and radiotherapy had been unsuccessful in preventing disease progression, and the patient developed hepatic metastases. As the tumor expressed a high level of estrogen receptor, treatment with fulvestrant 250 mg/month was initiated. **Results:** 25 months after commencing fulvestrant treatment, the tumor had decreased in size to 4.8 × 3.5 × 3.2 cm, and the hepatic metastases were no longer detectable. Throughout treatment, the patient maintained a Karnofsky performance index of 90%. **Conclusion:** We suggest that fulvestrant may be an active and well-tolerated treatment option for patients with estrogen receptor-positive advanced uterine cancer.

Schlüsselwörter

Endometriumkarzinom, fortgeschrittenes · Fulvestrant · Antihormontherapie · Lebermetastasen

Zusammenfassung

Hintergrund: Das fortgeschrittene Endometriumkarzinom ist weiterhin eine Herausforderung für onkologisch tätige Ärztinnen und Ärzte. Die Patientinnen haben eine schlechte Prognose mit einer mittleren Überlebensdauer von weniger als einem Jahr. Im folgenden Fallbericht wird die erfolgreiche Therapie einer Patientin mit einem fortgeschrittenen Endometriumkarzinom mittels des Antiöstrogens Fulvestrant präsentiert. **Fallbericht:** Bei einer 64-jährigen Patientin wurde ein fortgeschrittenes Endometriumkarzinom mit einer Größe von 7,0 × 6,0 × 5,5 cm und einer Infiltration der Harnblase diagnostiziert. Eine durchgeführte Chemo- und Strahlentherapie konnte einen Progress des Primärtumors nicht verhindern und die Patientin entwickelte Lebermetastasen. Aufgrund einer Östrogenrezeptor-Expression des Tumors wurde die Behandlung mit Fulvestrant 250 mg/Monat eingeleitet. **Ergebnisse:** Nach Behandlung mit Fulvestrant über 25 Monate konnte eine Regression des Primärtumors auf 4,8 × 3,5 × 3,2 cm erreicht werden. Die hepatische Metastasierung war nicht mehr nachweisbar. Während des gesamten Therapiezeitraumes blieb der Karnofsky-Index der Patientin bei 90%. **Schlussfolgerung:** Somit kann die Therapie mit Fulvestrant eine effektive und nebenwirkungsarme Behandlungsoption für Patientinnen mit einem östrogenrezeptorpositiven, fortgeschrittenen Endometriumkarzinom darstellen.

Introduction

Uterine cancer is the most common malignant neoplasm of the female genital tract and the 4th most common cancer in women [1]. Early-stage uterine cancer can usually be managed effectively [2]. However, advanced or recurrent uterine cancer is difficult to treat and shows a poor prognosis, with a median survival time of less than 1 year [3]. Recommended treatment comprises surgery (where appropriate) along with radiotherapy and chemotherapy [4], but the low response rates observed in the advanced setting reflect a need for new therapies.

Uterine cancer that expresses the estrogen (ER) and/or progesterone receptor (PgR) may be responsive to endocrine therapy [5]. Hormonal agents, in particular progestins [6], have been used to treat endometrial cancer for more than 40 years, although until recently response rates have remained unchanged [7]. Phase II studies have shown that the estrogen antagonist arzoxifene has antitumor activity in advanced endometrial cancer, demonstrating a response rate of 28% in 32 patients [8]. Preliminary evaluation of the non-steroidal aromatase inhibitor letrozole has also indicated that it may have potential in the treatment of endometrial cancer as well as low-grade endometrial stromal sarcoma [9].

The last few years have seen significant advances in the endocrine treatment of advanced breast cancer, one example being the introduction of the new ER antagonist fulvestrant (Faslodex®, AstraZeneca GmbH, Wedel, Germany) [10]. Such endocrine therapies may have a role to play in the treatment of other hormone-dependent cancers. Here, we report the successful use of fulvestrant in the treatment of a patient with ER-positive metastatic uterine cancer.

Case Report

This report follows the progress of a 64-year-old patient, who first presented in June 2003, and was diagnosed with advanced uterine cancer (cT4 N1 M0) by curettage. She had concomitant hyperthyroidism, varicosis and controlled hypertension. The following month (July 2003), an oophorectomy, staging laparotomy and lymph node biopsy of the aortocaval area were performed at the Women's Hospital of Erlangen University. Subsequent to surgery, in September 2003, a computed tomography (CT) scan showed a tumor of $7.0 \times 6.0 \times 5.5$ cm in size, and the laparotomy revealed 2 positive aortocaval lymph nodes, along with infiltration of the primary tumor into the bladder (fig. 1 a). Histological examination presented a tumor with partial squamous, partial mucinous and partial endometrioid differentiation (FIGO IVa, pT4a pN1 G2 R2). The same month, the patient received 1 cycle of docetaxel chemotherapy (100 mg/m^2) together with external beam radiotherapy to the pelvis and lymph drain region (median dose of 36.0 Gy to lumbar vertebra L1). This was followed by a further cycle of docetaxel chemotherapy (100 mg/m^2) along with radiotherapy to the pelvis (up to a median dose of 50.4 Gy to L5) in addition to a small volume boost irradiation of the para-aortic region (up to 40.3 Gy).

In October, the patient received intracavity high-dose rate (HDR) brachytherapy (median dose of 24.0 Gy in 6.0 Gy fractions). The following January, the patient received 2 cycles of docetaxel chemotherapy (100 mg/m^2). Docetaxel was administered as first-line chemotherapy

treatment analogous to the Uterus-4 study [5, 11], rather than the more commonly used platinum-based regimens. The choice for docetaxel was based on good personal experience with this regimen. At the first evaluation after chemotherapy (February 2004), the CT scan showed stable disease (fig. 1 b). The scan showed an inhomogeneous enhancing uterine tumor that was $6.6 \times 6.1 \times 5.7$ cm in size, and a hypodense hepatic lesion indicating possible metastasis ($1.5 \times 1.3 \times 1.0$ cm in the liver segment VII). Immunohistochemical analysis of the tumor had revealed a high level of expression of ER, and in light of this (and the suspected liver metastasis), the decision was made to initiate fulvestrant therapy at the standard dose of 250 mg/month (off-label use), commencing at the end of March 2004. Prior to this, ultrasonography revealed a stable pelvic tumor of $6.5 \times 6.1 \times 4.5$ cm in size. The first evaluation of the tumor by ultrasonography, after the initiation of fulvestrant (May 2004), revealed a stable pelvic tumor that was $5.0 \times 5.2 \times 3.7$ cm in size. The second (June 2004) and third (August 2004) evaluations (both by ultrasonography) revealed the tumor to be $6.1 \times 4.4 \times 3.8$ cm and $3.5 \times 3.3 \times 4.0$ cm in size, respectively, with no evidence of liver metastases or suspect structures.

The 4th evaluation (November 2004) was performed by CT scan, and once again showed that the uterine tumor had decreased to $6.0 \times 5.0 \times 4.3$ cm and that the hepatic lesion was no longer evident (fig. 1 c). At the 5th evaluation (February 2005), the pelvic lesion was no longer detectable by ultrasound, and therefore a control evaluation was performed by CT scan (March 2005). This scan showed that the tumor had decreased to $5.5 \times 4.6 \times 4.1$ cm in size, and demonstrated further remission. The 6th evaluation (July 2005), again performed by CT scan, showed that the uterine tumor had decreased to $5.5 \times 4.3 \times 3.6$ cm.

The most recent CT scans revealed that the uterine tumor had decreased in size to $5.0 \times 3.5 \times 3.4$ cm in November 2005 (fig. 1 d) and had shrunk to $4.8 \times 3.5 \times 3.2$ cm in April 2006. No new metastasis of the liver was detected. As of April 2006, fulvestrant therapy was ongoing and the patient was asymptomatic, generally in good health, and no serious adverse events had occurred. She experienced a weight gain of 32 kg during fulvestrant treatment, but had previously lost 14 kg during radiotherapy. This is representative of the patient returning to her former weight. Moreover, a Karnofsky performance index of 90% was maintained throughout fulvestrant treatment, reflecting the patients' good quality of life.

Discussion

Uterine cancer usually presents as stage I disease and can be managed effectively by extrafascial total hysterectomy with bilateral salpingo-oophorectomy [12]. However, the prognosis for advanced or recurrent uterine cancer is poor [13]. As uterine tumors arise from hormone-responsive tissue, some of these malignancies express hormone receptors and are therefore potentially responsive to endocrine therapy. Whilst some small studies [14–16] and phase II trials [17] have been published investigating this therapeutic avenue, there remains a need for further investigations.

In this case study, we demonstrated the successful treatment of metastatic uterine cancer with fulvestrant – a new ER antagonist with no agonist effects. At the time of fulvestrant administration, our patient also had a hepatic lesion. As has previously been noted, the liver is a common site of metastases for women with uterine cancer [18]. Our patient responded well to treatment for over 2 years, experiencing no serious adverse events and a stable Karnofsky performance index of 90%. The decision not to administer progestins was based

Fig. 1. Abdominal CT scan images showing response to treatment: **a** initial scan (September 2003); **b** pre-fulvestrant stable pelvic tumor with suspected hepatic metastases (February 2004); **c** effect of 8 months of fulvestrant treatment (November 2004), stable pelvic tumor and hepatic metastases no longer detectable; **d** effect of 21 months of fulvestrant treatment (November 2005), remission of the pelvic tumor, hepatic metastases not detectable.

mainly on their tolerability profile. These agents are associated with weight gain [19, 20] and may increase risk of thrombosis, particularly in those with other risk factors [21]. Response rates in patients with metastatic uterine cancer are also generally low [22]. Our patient had pre-existing hypertension and varicosis and was also overweight. Therefore, she was not considered suitable for progestin therapy. Although this was an off-label use, fulvestrant was chosen as this patient's first-line hormonal treatment based on the positive experience we had of using fulvestrant during the AGO Uterus-5 study. This is an open, multicenter phase II study assessing the efficacy and tolerability of fulvestrant 250 mg/month in the treatment of recurrent or metastatic endometrial carcinoma (www.ago-online.org; www.clinicaltrials.gov/ct/show/NCT00006903?order=1).

Some endocrine agents, e.g. tamoxifen, have weak estrogen agonist properties that can cause endometrial cell proliferation [23], perhaps making them less attractive options for the treatment of uterine cancer [24, 25]. Fulvestrant, in contrast, lacks estrogen agonist activity [26], and has been shown to block the growth of the endometrium in ovariectomized estrogen-treated monkeys [27]. Moreover fulvestrant inhibits the growth of EnCa101 carcinoma xenografts (derived from an ER-positive, well-differentiated human endometrial tumor) implanted in thymectomized mice [28], which gave an early suggestion of its potential in this setting.

Fulvestrant also offers the potential of durable efficacy, with phase III studies showing a median duration of response of 16.7 months in patients with tamoxifen-resistant advanced breast cancer [10]. The durable efficacy of fulvestrant observed in such clinical trials [10] is comparable with the prolonged response observed in our study. Additionally, fulvestrant has been shown to provide a similar quality of life to tamoxifen and anastrozole [10, 29]. Also, in line with clinical trial data [10, 29], fulvestrant was well tolerated by our patient. The restoration of the patient's former weight has not previously been reported.

2 phase II trials are currently underway investigating the activity of fulvestrant in endometrial carcinoma, one being the previously mentioned AGO Uterus-5 study. The Gynecologic Oncology Group (GOG) is also investigating the activity of fulvestrant in patients with recurrent, persistent or metastatic ER-positive and ER-negative endometrial carcinoma (www.clinicaltrials.gov/ct/show/NCT00006903). In addition, several phase III trials in patients with advanced breast cancer are ongoing that utilize fulvestrant loading-dose regimens (500 mg on day 0, 250 mg on days 14 and 28, 250 mg/month thereafter), which may result in a shorter time to response [30]. Should such regimens prove effective and well tolerated, they may also be considered in the metastatic uterine cancer setting.

The successful use of fulvestrant in an endocrine therapy-naïve patient was reported here. Although chemo- and radio-

therapy had failed to delay progression, fulvestrant treatment resulted in remission of the primary tumor and hepatic metastasis, a substantial period of stable disease and a good quality of life, as reported by the patient. Fulvestrant has previously been shown to be effective in the treatment of patients with advanced breast cancer [31] and is currently licensed for use in patients with breast cancer recurrence or progression following antiestrogen failure. Should the results of ongoing trials be positive, fulvestrant may offer patients with hormone recep-

tor-positive metastatic uterine cancer an exciting new treatment option.

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