PET imaging of ER expression in endometrial stromal sarcoma

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ABSTRACT

Although the majority of endometrial stromal sarcomas (ESS) express the estrogen receptor (ER), data on the efficacy of ER-targeted therapies are scarce. Using PubMed search engine we identified nine case reports and small series in a total of 25 patients reporting on the efficacy of palliative ER-targeted therapies. Literature supports the efficacy of aromatase inhibitors after the failure of progestins, but not of the partial ER antagonist tamoxifen. Fulvestrant is a pure ER antagonist with a distinct mechanism, of which efficacy has not yet been reported in ESS. We present a patient that underwent positron emission tomography and computed tomography (PET/CT) of ER expression with the tracer $^{18}$F-fluoroestradiol ($^{18}$F-FES). High levels of ER expression provided a rationale for fulvestrant therapy. $^{18}$F-FES-PET/CT was repeated after 6 months and indicated a strong decrease in tumor $^{18}$F-FES uptake and 15% reduction in tumor diameters according to Response Evaluation Criteria in Solid Tumors (RECIST).
INTRODUCTION

Sarcomas comprise ~4% of all uterine cancers. Out of these, only 9% are of the endometrial stromal sarcoma (ESS) subtype, i.e. 0.4% of all uterine cancers. Formerly, a division between low-grade and high-grade ESS was made, but the latter is now regarded a distinct subtype classified as poorly or undifferentiated uterine sarcoma.

ESS is an indolent growing tumor with a favorable prognosis. Five-year survival is 90% for patients presenting with stage I disease and 37-64% for stage III-IV. The majority (60-80%) of patients present with low stage disease for which hysterectomy with bilateral salpingo-oophorectomy is the standard treatment. For higher stage disease (III/IV), more extensive surgery is indicated, and even metastasectomy should be considered in case of distant metastases.

ESS tumors express the estrogen receptor (ER) and progesterone receptor in 40-100% of the cases. Therefore, hormone receptors form a potential target for adjuvant and palliative therapy. Two retrospective series have suggested a reduction in recurrence rate in patients treated with adjuvant progestins. However, it is unclear which patients would benefit from adjuvant hormonal therapy and how long it should be continued. The latter is especially relevant since recurrences tend to occur after a long interval, with a median time to recurrence of 65 months for stage I disease.

For recurrent and metastatic disease, systemic therapies are valuable as (neo)adjuvant therapy combined with cytoreductive surgery, or as palliative treatment. Most evidence to date is available for the use of progestins, which can induce objective tumor responses in up to 76% of the patients. There is currently no consensus on which treatments are effective after the failure of progestins, but ER-targeted therapies may well be of value.

We present a patient with ESS that was extensively pretreated. Molecular imaging of ER expression was performed by positron emission tomography (PET) with the tracer 18F-fluoroestradiol (18F-FES). Subsequently therapy with the ER down-regulator fulvestrant was initiated. In addition, we provide a systematic review of the literature evaluating the evidence for ER-targeted therapies in ESS.

CASE REPORT

A 44-year-old woman was referred to our hospital in 1994. She had been diagnosed with a low-grade ESS of the uterus in 1983 for which she had refused surgery. Systemic therapy with megestrol acetate 200 mg twice daily was initiated. In 1994 the patient was admitted to the gynecology ward of our hospital with progressive vaginal bleeding and
bowel obstruction. Cytoreductive surgery was performed including hysterectomy and bilateral salpingo-oophorectomy. Histological examination confirmed the presence of low-grade ESS (figure 1). Complete debulking could not be achieved and megestrol acetate was continued which led to a radiologic complete response. There was no evidence of disease until in November 2002 an intra-abdominal cystic mass was detected on MRI. The patient underwent complete cytoreductive surgery. Pathologic investigation of the tumor reported oval-shaped tumor cells with small nucleoli in the omentum and the cystic tumor with a morphology comparable to the earlier (low-grade) ESS. Tumor ER and PR staining was however repeatedly negative. Despite negativity in hormone receptors, megestrol acetate was continued given the earlier disease control. In 2005, progression on megestrol acetate was noted with local recurrence, mesenterial metastases, metastases on the peritoneal surface of the liver and lung metastases. Tamoxifen 20 mg once daily was initiated, which the patient stopped on her own initiative after 4 weeks of therapy due to side effects. She did not receive antitumor therapy thereafter until she developed pain symptoms in March.
2010 and anastrozole 1 mg once daily was started. Computed tomography (CT) scan after 6 months indicated stable disease.

In February 2012 extensive progression was noted on CT-scan with target lesion diameter increasing from 35 mm to 65 mm by Response Evaluation Criteria in Solid Tumors (RECIST). Evidence-based therapies were no longer available. To evaluate whether off-label ER-targeted therapy would be a potential option, the patient was referred for molecular imaging of ER expression by ¹⁸F-FES-PET/CT (Siemens CTI), as described previously. In contrast to the earlier immunohistochemistry, ¹⁸F-FES-PET/CT suggested ER positivity in pulmonary metastases, multiple lymph nodes, a parenchymal liver metastasis and pelvic masses. ¹⁸F-FES uptake was quantified in a total of 5 lesions according to the European Association of Nuclear Medicine criteria (maximum standardized uptake value [SUV\text{max}]). Tumor ¹⁸F-FES uptake was higher than generally observed in ER positive breast cancer patients (SUV\text{max} 11.8 vs. 5.9). Based on ¹⁸F-FES-PET results, off-label treatment with the pure ER antagonist fulvestrant was initiated, according to current practice in breast cancer (per intramuscular injections of 500 mg q4w plus a 500 mg loading dose on day 14). A clinical response was noted with subjective relief of pain and abdominal complaints. ¹⁸F-FES-PET/CT-scan was repeated after 6 months of therapy and indicated a strong decrease in ¹⁸F-FES binding. Average pre- and post-treatment ¹⁸F-FES uptake was 11.8 vs. 4.1 (-65%), supporting blockage and/or degradation of the ER by fulvestrant. CT-scan revealed stable disease (-15% according to RECIST v1.1). The patient is now alive with disease for 29 years since primary diagnosis. Representative pre- and post-treatment ¹⁸F-FES-PET/CT images are shown in figure 2 and treatment overview in table 1. Informed consent for publication was obtained from the patient.

DISCUSSION

ESS is a tumor type that has a high relapse rate despite its indolent growth. Patients will therefore often require systemic therapy at some point. We systematically reviewed the available literature to evaluate the evidence for ER-targeted therapy after progestin failure for metastatic ESS.

Data of nine case reports and small series in a total of 25 subjects with metastatic ESS, that allowed evaluation of the efficacy of ER-targeted therapies, were retrieved by our search strategy (table 2). There is limited evidence for efficacy of the non-steroidal aromatase inhibitors letrozole and anastrozole. In these reports, 19 of 22 (86%) patients experienced clinical benefit (objective tumor response or stable disease ≥6 months), and 15 of 22 (68%) objective (radiologic) tumor response. The latter illustrates that the observed treatment effects are not simply a result of the indolent course of disease. The response
Table 1: Treatments of the presented patient

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Efficacy</th>
<th>Response duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Megestrol acetate 200 mg bid</td>
<td>SD</td>
<td>84</td>
</tr>
<tr>
<td>(2) Megestrol acetate (following surgery) 160 mg od</td>
<td>CR</td>
<td>96</td>
</tr>
<tr>
<td>(3) Tamoxifen 20 mg od</td>
<td>n.a.</td>
<td>-</td>
</tr>
<tr>
<td>(4) Anastrozole 1 mg od</td>
<td>SD</td>
<td>23</td>
</tr>
<tr>
<td>(5) Fulvestrant 500 mg q4w plus 500 mg at day 14</td>
<td>SD</td>
<td>14+</td>
</tr>
</tbody>
</table>

Abbreviations: od=once daily; bid=twice daily; q4w=every 4 weeks n.a.=not available (due to discontinuation); SD = stable disease; CR = complete response; + indicates an ongoing response at the time of analysis.

rate observed on aromatase inhibitors is slightly higher than that on progestins, although no comparative studies have been performed. Given the more widespread experience with progestins for ESS, the non-steroidal aromatase inhibitors should especially be considered as 2nd line therapy until more data are available.

For the steroidal aromatase inhibitor exemestane only one case is reported, in which a partial response was observed after the failure of anastrozole. There is a biological
**Table 2:** Estrogen receptor directed therapies in recurrent ESS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Line*</th>
<th>OR</th>
<th>CBR</th>
<th>Duration (months)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole or anastrozole</td>
<td>14</td>
<td>1st</td>
<td>8 (57)</td>
<td>11 (79)</td>
<td>30+</td>
<td>122,125–127,129,130</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>2nd</td>
<td>6 (83)</td>
<td>7 (100)</td>
<td>34+</td>
<td>122,126,127,129,132,133</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3rd</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>9</td>
<td>126</td>
</tr>
<tr>
<td>Exemestane</td>
<td>1</td>
<td>2nd</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>6+</td>
<td>126</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>1</td>
<td>1st</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2nd</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>124</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>1</td>
<td>3rd</td>
<td>0</td>
<td>1 (100)</td>
<td>14+</td>
<td>This manuscript</td>
</tr>
</tbody>
</table>

*Chemotherapy regimens and adjuvant therapies excluded.

Data on the use of the selective ER modulator tamoxifen are largely inconsistent. Where according to the National Comprehensive Cancer Network (NCCN) guideline for uterine cancer tamoxifen may be considered, studies suggest that tamoxifen may actually increase the risk for developing ESS and negatively impact its disease course.\(^1\)\(^2\),\(^12\),\(^28\),\(^13\),\(^5\)–\(^14\) Tamoxifen is also associated with an increased risk of endometrial carcinoma, hyperplasia and polyps. This can be explained by the fact that tamoxifen, in contrast to its antagonistic activity in breast cancer, exerts agonistic effects in endometrial tissue. This tissue-specific mechanism of action is a result of differentially expressed co-regulatory proteins in endometrial cells compared to breast cancer cells. Whereas tamoxifen results in the recruitment of co-repressors at the target promoter site in breast cancer cells, in endometrial cells tamoxifen induces the recruitment of co-activators.\(^14\),\(^15\) This eventually leads to the transcription of genes responsible for increased proliferation and cell survival.

No report on the efficacy of the pure ER antagonist fulvestrant in ESS was retrieved by our search strategy. A negative publication bias, however, for unsuccessful administration of fulvestrant may exist. Fulvestrant binds irreversibly to the ER and induces a different conformation as compared to tamoxifen. This altered conformation results in inactive
complexes of the regions responsible for recruitment of co-activators. Indeed, fulvestrant has no known agonistic effects. In addition, fulvestrant increases the degradation of ER resulting in reduced expression levels. These characteristics provided a rationale for exploring fulvestrant therapy in the presented case.

We show for the first time the use of molecular imaging of ER expression in ESS, to provide a biological rationale for further exploration of ER-targeted therapies. The presented patient experienced progression after extensive pretreatment with endocrine agents, including treatment with a progestin and an aromatase inhibitor. Based on 18F-FES-PET results treatment with fulvestrant was initiated, which resulted in prolonged stable disease.

Although there are no trials in ESS that have shown the predictive value of ER expression for response to endocrine therapy, in other tumor types the predictive value of ER expression for response to endocrine therapy is well-established. Molecular imaging by 18F-FES-PET is a novel method to determine ER expression in vivo. In breast cancer studies, 18F-FES-PET showed ER positive metastases with high specificity. Also, 18F-FES-PET predicted response to endocrine therapies in a small series of breast cancer patients. Not all ESS tumors are positive for ER expression, and transition from ESS to poorly or undifferentiated uterine sarcomas has been described. 18F-FES-PET may therefore be valuable to select ESS patients eligible for ER-targeted therapies, by providing up-to-date information on ER status of the metastases. Interestingly, our patient had an earlier ER negative tumor by immunohistochemistry, while 18F-FES-PET was positive. Although we are unable to fully explain the discordance, changes in ER expression during disease progression have been observed in other tumor types. Alternatively, histology may generate sampling errors due to heterogeneity of ER expression or render false-negative results. Nevertheless, the benefit obtained from fulvestrant therapy supported the findings on 18F-FES-PET.

**CONCLUSION**

Molecular imaging of ER expression in a patient with metastatic ESS provided insight in the relevance of the ER in this disease. Based on a systematic review of the literature, patients with metastatic ESS that progress following progestin therapy should be treated with a steroidal aromatase inhibitor. Non-cross-resistance with the non-steroidal aromatase inhibitor exemestane provides a biological rationale for this treatment, although clinical data on its efficacy in ESS are lacking. Given our results, the selective ER down-regulator fulvestrant may also be added to the endocrine armamentarium. The rarity of this disease makes it challenging to perform robust prospective trials, although such initiatives would obviously be applauded.
SEARCH STRATEGY

A review of the literature was undertaken to evaluate endocrine treatment options for ESS and their efficacy. Using PubMed search engine and the keywords “endometrial stromal sarcoma” AND “low” AND “grade”, 290 papers were selected. Thereafter articles were filtered for 1) full text, 2) written in English, and 3) published after 1970. Case reports, clinical studies and comparative studies were selected. No randomized trials were available. The titles and abstracts of the remaining 127 papers were manually screened for relevance.

A combination of the keywords “ESS” and “tamoxifen” or “anastrozole” or “letrozole” or “exemestane” or “fulvestrant” was used to identify remaining articles that were not detected by our first search strategy. Reports in which endocrine therapy was given as adjuvant therapy were excluded since these do not allow response evaluation.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest. Dr. Hospers received a research grant made available to the UMCG from AstraZeneca.

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