Management of Late Recurrence of a Low-grade Endometrial Stromal Sarcoma (LGESS): Treatment with Letrozole

K. KRAUSS1, C. BACHMANN1, J.T. HARTMANN2,5, K. SIEGMANN3, K. SOTLAR1, D. WALLWIENER1 and J. HUOBER1

1Department of Obstetrics and Gynecology, Eberhard-Karls-University Tuebingen, Calweistr. 7, D-72076 Tuebingen; 2Department of Medical Oncology, Hematology, Immunology, Rheumatology, Pulmology, Medical Center II, and 3Interdisciplinary Sarcoma Center, South West German Cancer Center, Eberhard-Karls-University Tuebingen, Otfrid-Mueller Str. 10, D-72076 Tuebingen; 4Department of Diagnostic Radiology and Imaging, Eberhard-Karls-University Tuebingen, Hoppe-Seyler Str. 3, D-72076 Tuebingen; 5Institute of Pathology, Eberhard-Karls-University Tuebingen, Liebermeisterstr. 8, D-72076 Tuebingen, Germany

Abstract. Low grade endometrial stromal sarcoma (LGESS) is a rare disease. LGESS usually expresses steroidal receptors and is regarded to be hormone-sensitive. Due to the rarity of the tumor, only few case series have been published so far. Here, we report the case of a 36-year-old woman who underwent an abdominal hysterectomy with bilateral salpingo-oophorectomy and adjuvant radiotherapy for a G1 LGESS in 1991. Twelve years later she presented to us with pelvic and peritoneal masses. The patient was treated with letrozole achieving a partial response which is lasting 39 months. Treatment is ongoing. Aromatase inhibitors represent an interesting treatment option for LGESS.

Introduction

Current treatment options for metastatic soft tissue sarcomas are limited and are associated with poor response rates. Therefore, new therapeutic agents as well as new forms of treatment with established agents are warranted to improve outcome in these patients. Endometrial stromal tumors are rare and account for about 10-15% of all uterine sarcomas. They are divided into three categories: a) benign endometrial stromal nodules; b) low-grade endometrial stromal sarcoma; and c) undifferentiated endometrial sarcoma. While virtually indistinguishable from stromal nodules on cytological or mitotic activity grounds, low-grade stromal sarcomas, as the critical feature, invade the surrounding myometrium or vascular structures. In contrast, undifferentiated endometrial sarcoma bears no histological resemblance to the endometrial stroma (1). Established risk factors for recurrence are the stage of disease at the time of diagnosis and exposure to estrogen, or even tamoxifen. Recurrent disease will develop, depending on the stage of the primary disease, in approximately 50% of the patients. Recurrences are also reported after long time intervals, e.g. more than 20 years after the initial diagnosis. They usually occur in the abdomen or pelvis but distant metastases have also been seen, mainly in the lung. Low-grade endometrial stromal sarcomas (LGESS) usually express steroidal receptors and are therefore potentially hormone-sensitive.

Case Report

Our patient, a 36-year-old woman, underwent an abdominal hysterectomy and bilateral adenectomy for a low-grade G1 [according to Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) (2)] endometrial stromal sarcoma. The tumor stage was classified as pT3 pNx M0. The histological examination revealed an LGESS with tumor infiltration of the connective tissue of the parametrium and invasion of the lymphatic vessels. Adjuvant irradiation of the pelvis with a total dose of 50.4 Gy was applied. The patient was free of disease until 2003, and had been on transdermal estrogen substitution from 1997 to February 2003. In January 2003, she reported recurrent left-sided abdominal pain in the lower quadrant and lower back pain. On an MRI scan of the
pelvis, a tissue formation in the recto-vaginal space and additionally suspicious peritoneal lesions in the mesenterium and on the abdominal wall were detected. The additional staging with a CT scan revealed multiple lung metastases with lesions up to 2.6 cm, a right-sided renal obstruction due to peritoneal lesions and a lesion within the left psoas muscle with infiltration of the spinal canal through the neuroforamen L 2/3 (Figure 1 A, C). This lesion was biopsied and confirmed as a metastasis of the known LGESS. The immunohistochemical profile was identical to that of the primary tumor diagnosed in 1991, revealing an expression of desmin, CD10 and CD99 at a low level. The tumor was negative for cytokeratin, actin, S100 protein, CD34 and CD117. The proliferation-associated antigen Ki-67 was expressed in 15% of the cells. Additionally, more than 80% of the tumor cells showed a strong nuclear expression of the estrogen and progesterone receptors (Figure 2).

Due to the highly positive hormone receptor status, an endocrine treatment with letrozole was initiated and a DJ-catheter was implanted to relieve the obstruction of the right kidney. Treatment with letrozole was effective and quickly reduced the pain. The DJ-catheter was therefore removed in May 2003, 3 months after the start of therapy with letrozole. After 39 months, the patient is in a status of partial remission and treatment is ongoing (Figure 1 B, D). Treatment with letrozole is well-tolerated without any serious side-effects. To prevent drug-induced osteoporosis, a bisphosphonate therapy was added.

The standard treatment for localized endometrial stromal sarcomas is an abdominal hysterectomy and bilateral salpingo-oophorectomy. As for all sarcomas of the uterus, debulking is recommended when an extra-uterine tumor is visible. In stage I disease, the diagnosis is often made postoperatively, by chance. Adjuvant radiation therapy is associated with a lower risk of local recurrences (3). Cytotoxic drugs commonly used in the palliative setting for metastatic disease, e.g. anthracyclines or ifosfamide, are usually restricted to high-grade subtypes. Undifferentiated endometrial sarcomas (UES) usually lack hormone receptor expression. They show a more aggressive clinical course and are associated with a much worse prognosis (4). In a report with 9 patients with UES and 15 patients with LGESS, the 5-year survival rate was 85% and 92% and the 5-year disease-free survival (DFS) was 0% and 84%, respectively (5). Tumor cells of LGESS resemble those of proliferative phase endometrial stroma and, likewise, usually express estrogen and progesterin receptors (6). In LGESS, adjuvant endocrine treatment

Figure 1. Multislice CT of the abdomen (A, B) and the chest (C, D) demonstrate a partial remission of the metastases within the left psoas muscle and in the lung during treatment with the aromatase inhibitor letrozole. A) January 2003, a hypervascularized tumor can be seen within the left psoas muscle infiltrating the spinal canal through the neuroforamen L 2/3 (arrow). B) After 5 months of therapy with letrozole, only a small residual tumor can be seen (arrow). C) The lung metastasis in the left lower lobe was detected in January 2003 with a diameter of 2.6 cm (arrow). D) Five months later, only a small cyst remained in the former tumor location (arrow).
with progestin might be a valuable option. In a retrospective analysis, recurrence developed in 4 of 13 patients who received adjuvant progestin therapy in contrast to 6 of 9 patients without adjuvant progestin therapy (7). This effect was not only confined to late-stage disease but could also be seen in stage I disease.

The importance of the hormonal influence in LGESS is also shown by an elevated recurrence risk through estrogens. In a small series, estrogen replacement therapy was related to a higher recurrence rate (recurrence in 4 of 5 patients), whereas patients with retained ovaries appeared to have a somewhat lower recurrence rate (recurrence in 4 of 8 patients) (7). In another report, the risk of recurrence was elevated even with conservation of the ovaries (recurrence in all 6 patients) (8). A recent paper reported 10 patients with recurrence of an LGESS (9). Estrogen replacement therapy was again seen as a risk factor, as well as treatment with tamoxifen. Even though these are small series, the data suggest an unfavourable influence of estrogens on the outcome of LGESS.

Several endocrine treatment options such as megestrol acetate, medroxyprogesterone acetate (MPA), amino-glutethimide and letrozole for recurrences of hormonestive LGESS are described in case reports (7, 9-12) (Table 1). Long-lasting treatment effects with complete remissions over 5 years and longer have been reported with MPA and aromatase inhibitors.

Treatment with letrozole induced a fast remission in our patient lasting for more than 3 years under continuing

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<th>CR</th>
<th>SD</th>
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<td>5/11</td>
<td>3/11</td>
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<td>Aromatase inhibitor (9-12)</td>
<td>6/9</td>
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PR, partial remission; CR, complete remission; SD, stable disease.

Figure 2. Histology of the metastatic tumor in the psoas muscle showed a low-grade endometrial stromal sarcoma (LGESS). A) Cellular tumor around some spiral artery-like vessels (H&E). B) Positive cytoplasmic and membrane staining for CD10. C) Low to intermediate proliferative activity (Ki-67). D) Strong nuclear expression of estrogen receptor (ER).
therapy with letrozole. Endocrine treatment with progestin or an aromatase inhibitor may be a reasonable treatment option for these patients.

References


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