Successful Use of Dydrogesterone as Maintenance Therapy in Recurrent Endometrial Stromal Sarcoma: A Case Report

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Endometrial stromal sarcoma is known to be a hormone-dependent tumor. Efficacy of hormonal therapy including high-dose progestins, aromatase inhibitors or gonadotropin-releasing hormone analogs has been reported. We report a case of recurrent endometrial stromal sarcoma, the tumor cells of which were strongly positive for CD10, estrogen and progesterone receptors. Although almost all of the pelvic tumors infiltrating the rectum or pelvic side wall remained, the patient is alive with slight disease 9 years and 6 months after the initial failure. During the treatment period of 4 years and 3 months, the patient was treated exclusively with dydrogesterone at a daily dose of 10 mg and the tumor clinically disappeared. Dydrogesterone at a daily dose of 10 mg may be effective in treating low-grade endometrial stromal sarcoma.

Key words: endometrial stromal sarcoma – dydrogesterone – hormonal therapy

INTRODUCTION

According to a report in 2012 based on the nationwide population-based Netherlands Cancer Registry, endometrial stromal sarcoma is the third most common uterine sarcoma (0.7/1 000 000) following leiomyosarcoma (4.2/1 000 000) and undifferentiated endometrial sarcoma (1.8/1 000 000) (1). A standard treatment for advanced or recurrent endometrial stromal sarcoma has not been established because of its low incidence. The therapeutic effect of radiation therapy for unresectable endometrial stromal sarcoma has been limited (2). There has also not been sufficient evidence for efficacy of chemotherapy (3). In contrast, the effectiveness of hormonal therapy (4), including high-dose progestins (5,6), aromatase inhibitors (7,8) or gonadotropin-releasing hormone analogs (GnRHAs) (9,10), has been reported despite there being side effects peculiar to each agent. Side effects of high-dose progestin therapy include weight gain, depression and thrombosis (11). Both aromatase inhibitors and GnRHAs inhibit estrogen receptor-mediated growth promotion by lowering estrogen levels. A long-term use of these agents results in postmenopausal vasomotor symptoms, vaginal dryness and osteoporosis.

Since endometrial stromal sarcoma is an indolent tumor, appropriate use of different agents with distinct side effects is important for long-term survival and maintenance of quality of life.

Dydrogesterone is relatively safe and well tolerated and does not exhibit the androgenic side effects that are common with some other progestins, such as medroxyprogesterone acetate. There has been no report on the benefit of dydrogesterone for endometrial stromal sarcoma. We encountered a patient with recurrent and unresectable endometrial stromal sarcoma who is alive with slight disease 9 years and 6 months after the initial failure. The patient was treated exclusively with dydrogesterone at a daily dose of 10 mg during the treatment period and the tumor clinically disappeared. It is possible that patients with recurrent endometrial stromal sarcoma will benefit from low-dose progesterone treatment.

CASE REPORT

A 55-year-old woman, gravida 3 and para 3, was admitted to the Hokkaido Cancer Center with the chief complaint of...
melena. Endoscopic examination of the rectosigmoid colon showed a bulge on half of the circumference of the lumen from the outside. Magnetic resonance imaging (MRI) revealed multiple solid masses in the pelvis (Fig. 1A and B). Speculum examination of the vaginal stump showed no abnormal findings. A few subcutaneous tumors with irregular surfaces were found on the left upper thigh on physical examination. The patient’s serum level of CA-125 was 33 U/ml (normal value: 35.0 U/ml). Serum levels of CA19-9 (normal value: 37.0 U/ml) and carcinoembryonic antigen (CEA) (normal value: 2.5 ng/ml) were normal. The patient underwent surgical treatment in October 2004. Colostomy was performed due to the unresectable status of pelvic tumors (Fig. 1C). In addition, sampling of a pelvic mass and removal of subcutaneous tumors in the left thigh were performed (Fig. 1D). Pathologic examination of subcutaneous tumors in the left thigh revealed multiple cellular tumors with irregularly infiltrating margins (Fig. 2A). The cells of the tumor were uniform and resembled stromal cells of normal proliferative phase endometrium, and the vascular pattern of the tumors was distinctive, comprising small blood vessels (Fig. 2B). Pathologic examination of a pelvic tumor also showed component cells similar to those in the left thigh specimen. Immunohisto-chemistry revealed that tumor cells were negative for cytokeratin, c-kit, S-100 and desmin, focally and weakly positive for smooth muscle actin, and strongly positive for vimentin, CD10 (Fig. 2C), estrogen (Fig. 2D) and progesterone receptors (Fig. 2E). The patient had a past history of vaginal hysterectomy for myoma uteri at another hospital 9 years before. A pathologic review of the specimen of the uterus revealed the presence of a tumor uniformly and densely consisting of short spindle cells (Fig. 2F), with a small portion of the margin slightly infiltrating into the myometrium (Fig. 2G). There was no evidence of adenomyosis or endometriosis. Morphological characteristics of the uterine tumor were similar to those of the tumors in the pelvic cavity and the thigh. Therefore, she was diagnosed with recurrent endometrial stromal sarcoma in the pelvis and the left thigh. The patient received six cycles of combination chemotherapy consisting of docetaxel (60 mg/m²) and carboplatin (AUC = 5) concomitant with the use of leuprolide acetate (3.75 mg/body) every 4 weeks. An MRI revealed that all of the masses were greatly reduced in size (Fig. 3A). She received additional three courses of leuprolide acetate (3.75 mg/body) every 4 weeks, and MRI revealed that all of the tumors were further reduced in size (Fig. 3B). However, she felt stiffness in the joints of the fingers and leuprolide acetate medication was stopped. After that, she started taking dydrogesterone at a daily dose of 10 mg in August 2005. No other treatment including radiation therapy, chemotherapy and other hormonal therapy was given. One year later, the main tumor was further reduced in size and many tumors were no longer detectable (Fig. 3C). She was treated with dydrogesterone for a total of 4 years and 3 months until November 2009, during which MRI did not show any tumors (Fig. 3D). Three years after the last hormonal therapy, computed tomography demonstrated tumor regrowth in November 2012, and high-dose medroxyprogesterone therapy was initiated at a daily dose of 400 mg. The patients are now alive with slight disease but in good health.

Figure 1. T₂-enhanced magnetic resonance imaging (MRI) demonstrated multiple masses occupying the back of the pelvic cavity (A and B). Recurrent tumors disseminating in the rectum (arrow) and bilateral ovarian tumors invading the pelvic wall (arrowhead) were demonstrated at the time of surgery (C). Recurrent tumor in the subcutaneous tissue of the left upper thigh was removed (D).
DISCUSSION

Although successful hormonal treatment, including high-dose progestins (5,6), aromatase inhibitors (7,8) or GnRHa (9,10), has been reported in cases of advanced or recurrent endometrial stromal sarcoma, the tumor is known to be an indolent tumor. Therefore, long-term administration of these agents is needed and attention should be paid to side effects.

It is well known that side effects of high-dose progestin therapy are thrombo-embolic complications, weight gain and depression (11). In a dose-response study on oral medroxyprogesterone acetate for the treatment of advanced or recurrent endometrial cancer by the Gynecologic Oncology Group, the most frequent adverse event was thrombophlebitis, which occurred in 5% of the patients in the 200 mg/day group and in 4% of the patients in the 1000 mg/day group (12). Since the frequency of thrombo-embolic complications was lower than expected, the high-dose progestin therapy was considered to be tolerable, but the median overall survival periods were 11 months for the low-dose group and 7 months for the high-dose group. In a nutshell, the administration period of medroxyprogesterone acetate was short in that study. There have been few reports on side effects of long-term high-dose medroxyprogesterone acetate therapy. In 2012, Mizuno et al. reported the effects of long-term high-dose medroxyprogesterone acetate therapy (6). In that study, six patients received high-dose medroxyprogesterone acetate with an anti-platelet agent (aspirin, 100 mg/day) for long periods ranging from 28 to 92 months (median period, 63 months), and there were no thrombo-embolic complications. The use of an anti-platelet agent might reduce the incidence of thrombo-embolic complications.

Figure 2. Microscopic findings of the subcutaneous tumor in the left thigh demonstrated that the tumor had an irregularly infiltrating margin (A, hematoxylin and eosin ×2) with cells of the tumor resembling stromal cells of normal proliferative phase endometrium and comprising small blood vessels (B, hematoxylin and eosin ×20). Immunohistochemistry revealed that tumor cells were strongly positive for CD10 (C), estrogen receptor (D) and progesterone receptor (E). Re-examination of the uterus removed 9 years ago revealed a tumor consisting of dense growth of short spindle cells, consistent with the endometrial stromal sarcoma (F, hematoxylin and eosin ×20). A small portion of the margin slightly infiltrated into the myometrium (G, hematoxylin and eosin ×4).
complications during high-dose medroxyprogesterone acetate therapy.

It is known that side effects of treatment with an aromatase inhibitor are musculoskeletal stiffness and pain, fatigue, hot flushes and nausea (7,13). In 2011, Fontein et al. reported a high level of non-compliance with letrozole in breast cancer patients (13). In that study, the overall non-compliance probability was 18.4% within the 2.5-year follow-up period, and the most frequent adverse event was a musculoskeletal-related symptom. Adverse effects of a GnRH agonist also include symptoms caused by a lack of estrogen. A long-term use of a GnRH agonist causes osteoporosis (14,15). In the present case, a total of nine courses of leuprolide acetate (3.75 mg/body) every 4 weeks caused stiff joints of the fingers. Chemotherapy consisting of docetaxel and carboplatin, of course, may have caused the neurotoxicity. However, the patient decided to discontinue treatment with leuprolide acetate despite the effectiveness of the treatment.

Dydrogesterone is a hormonally active, non-androgenic synthetic steroid that was developed in the 1950s (16). It has a molecular structure almost identical to that of natural progesterone, which accounts for the lack of estrogenic, androgenic glucocorticoid and mineralocorticoid properties of dydrogesterone (17). Therefore, dydrogesterone is more advantageous than other progestins, such as medroxyprogesterone acetate, in view of side effects when long-term medication or repeated courses of treatment are needed (17–19). In short, dydrogesterone is suitable for the treatment of endometriosis (18) or benign breast disease (19), especially when patients desire to become pregnant. There has been no report on the efficacy of dydrogesterone in endometrial stromal sarcoma. In the present case, the choice of dydrogesterone was a product of compromise between the patient’s discontent against adverse effects of medication and the physician’s concern over regrowth of the tumor in the pelvis. Therefore, the authors cannot give a reasonable explanation for the choice of dydrogesterone. Of course, the first choice of hormone therapy in endometrial stromal sarcoma would be high-dose progestin, an aromatase inhibitor or a GnRH agonist. When side effects of these agents result in patients discontinuing the treatment and tumors still remain, subsequent dydrogesterone medication may control regrowth of residual tumors.

Conflict of interest statement

None declared.

References


