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Systemic therapy for endometrial stromal sarcomas: current treatment options

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ABSTRACT

Uterine endometrial stromal sarcomas including true low-grade endometrial stromal sarcoma (LG-ESS) and high-grade (HG-ESS) or undifferentiated endometrial sarcoma (UES) constitute a group of rare, aggressive malignancies. Most LG-ESSs express steroid receptors. Surgery is the principal primary therapy for endometrial stromal sarcomas and should be considered in all cases. These malignancies are relatively radio- and chemoresistant. Chemotherapy is used in recurrent and advanced HG-ESS and UES. Currently, the combination of gemcitabine and docetaxel is considered the most effective regimen, but at the expense of substantial toxicity. In steroid receptor positive advanced LG-ESS hormonal therapy, mainly with progestins, allows in some patients for a long-term survival. Aromatase inhibitors seem to be equally effective as first- and subsequent-line of treatment, and are well tolerated. The role of molecular-targeted therapies in endometrial stromal sarcomas remains to be established.

Key words: endometrial stromal sarcoma, chemotherapy, endocrine therapy, targeted therapy

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INTRODUCTION

Endometrial stromal sarcomas are rare tumors of pure mesenchymal origin, comprising approximately 0.2% of all uterine malignancies and 10–25% of all uterine sarcomas [1]. According to the World Health Organisation (WHO) classification from 2014, there is a distinction between true endometrial stromal sarcoma (ESS), also known as a low-grade endometrial stromal sarcoma (LG-ESS), and high-grade (HG-ESS) or undifferentiated endometrial or stromal sarcoma (UES). These subtypes are defined based on clinical and pathologic features.

The most sensitive marker for ESS is a CD10-antigen and a cytogenetic hallmark of this tumor is a t(7;17)(p15;q21) (*JAZF1-JJAZ1*) rearrangement [1–3]. ESSs are relatively more common than non-LG-ESSs, with most cases occurring before menopause. ESS is generally a slow-growing malignancy with an indolent clinical course. In most women ESS is diagnosed in an early stage, and 65–86% of reported cases are confined to the uterus. The reported 5-year overall survival (OS) rates are in the range of 80–100%, but 40–50% of patients even after 20 years will develop relapse, which is typically located in the pelvis, abdomen or lungs [1, 4]. In contrast, HG-ESS, usually characterized by the t(10;17)(q22;p13) translocation (*YWHAE-FAM22* rearrangements), and UES which exhibits no specific translocation pattern, have typical for sarcomas, aggressive clinical behavior [5, 6]. Of note, molecular diagnostics is helpful but not essential for the diagnosis of non-LG-ESS. Poor prognosis, similar to that in leiomyosarcoma (LMS), is a result of its high recurrence propensity, both locally and at distant sites [5]. Treatment results of non-LG-ESS are relatively poor, with merely 25–55% five year survival. Cases of extrauterine endometrial stromal sarcoma (typically developing from endometriosis) and affecting young pregnant women have been reported [7, 8].

Surgery consisting of total hysterectomy and bilateral salpingo-ophorectomy is the principal therapy of early endometrial stromal sarcomas, whereas the role of elective lymphadenectomy is not well established. Ovary-sparing surgery in young women with early ESS is a matter of debate, as this procedure is associated with relatively high risk of local recurrence [9]. The role of postoperative radiotherapy and hormonal therapy in ESS is also not well established [10–12]. Cytoreductive surgery should also be considered in all metastatic and recurrent cases. This management

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is an independent predictor of better survival after ESS recurrence [13].

Due to the rarity of endometrial stromal sarcomas, the current knowledge is mainly based on case reports. We present here contemporary systemic treatment options for advanced ESS and non-LG-ESS.

CHEMOTHERAPY

Chemotherapy, in addition to palliative radiotherapy and surgery has been used in recurrent and advanced non-LG-ESS, and in hormone-unresponsive ESS cases. There has been only one prospective phase II study investigating the role of first-line chemotherapy in patients with endometrial stromal sarcomas, conducted by Gynecologic Oncology Group (GOG) [14]. This study included 31 patients with primary advanced or recurrent disease and used ifosfamide at a dose of 1.5 g/m^2 given on days 1–5, every 3 weeks. Overall 33% of patients responded to treatment, 14% with complete and 19% with partial remission, respectively. The median progression-free survival in the entire group was 3 months.

Chemotherapy includes compounds used in other soft-tissue sarcomas, such as anthracyclines, dacarbazine, vinorelbine, gemcitabine, docetaxel and temozolomide. This cytotoxis are administered alone or in doublets, eg. docetaxel/gemcitabine, doxorubicin/ifosfamide, doxorubicin/dacarbazine, gemcitabine/dacarbazine or gemcitabine/vinorelbine. The combination of gemcitabine and docetaxel as both the first- and second-line therapy in LMS was investigated in two phase II trials conducted by GOG [15, 16]. This regimen included 900 mg/m^2 of gemcitabine on days 1 and 8 plus docetaxel 100 mg/m^2 on day 8, given every 3 weeks with a granulocyte colony-stimulating factor. The response rate of 36% reported in the first-line setting compares favorably to 20–30% response rates observed with single-agent doxorubicin (typically at doses of about 60 mg/m^2 every 3 weeks). A case of long-term complete remission of ESS following 12 cycles of gemcitabine plus docetaxel was reported [17]. Toxicities accompanying this regimen include myelosuppression, fatigue and fluid retention but, as opposed to anthracycline-based regimens, may be continued for a longer period of time without limiting cardiac toxicity. More recently, a partial regression was reported in one out of three patients with non-LG-ESS treated with trabectedin as a salvage treatment [18]. No effect was reported in a non-LG-ESS case treated with paclitaxel and carboplatin [19].

ENDOCRINE THERAPY

Almost 80% of ESS express estrogen alpha (ER) and progesterone receptors (PgR) [1]. The PgR A is the dominant isoform in primary ESS, whereas, recurrent tumors are characterized by PgR B expression. Additionally, most ESS cases show the intratumoral immunohistochemical expression of aromatase and gonadotropin releasing hormone (GnRH) receptor.

In steroid receptor positive advanced ESSs, considered to be radio- and chemotherapy resistant, hormonal therapy constitutes a standard management which improve long-term survival. This therapy induces a proportion of durable responses or disease stabilizations. There are no specific guidelines specifying particular endocrine therapies and their sequence. Several case reports and small series demonstrated long-term benefit of progestin treatments including megestrol acetate or medroxyprogesterone acetate (MPA) used at doses of 200 mg up to even 1000 mg/day in continuous or intermittent schedules [20–22]. Progestins are used as the first-line treatment, after prior chemotherapy and as an adjunct to complete resection of metastatic lesions. Apart from weight gain, side-effects of long-term high-dose progestin therapy include increased risk of severe depression and thromboembolic complications [1]. Hence, currently the third generation aromatase inhibitors (AIs) and GnRH analogues have become alternative endocrine treatments for ESS.

Data on the efficacy of AIs for ESS are scarce, with most published studies being case reports [23–30]. There is a report of complete responses lasting for more than 7 and 14 years in two patients with lung metastases treated with aminoglutethimide (500 mg bid) [28]. Another study reported two year disease stabilization in ESS with sex-cord compound, treated with anastrozole and megestrol acetate [25]. Letrozole, another most frequently reported non-steroid AI, was used both in the first-line therapy and after failure on progestins and tamoxifen. Responses were usually partial, however complete responses were also reported. These include a patient with lung metastases who achieved a complete response lasting for more than 27 months after sequential therapy with letrozole (for 8 months) and anastrozole [23]. In a series of five patients treated with letrozole, durable partial response was obtained in all three cases administered AI as primary treatment and in one treated with MPA [26]. In another series of five patients treated with letrozole for unresectable peritoneal recurrent ESS two patients achieved complete responses lasting for 96 and 87 months [30]. These tumors were positive for ER, PgR and CD10, and negative for CD117. Good tolerance of letrozole was reported in all studies.

The efficacy of GnRH analogues and their role in complete estrogen deprivation remains to be established [31, 32]. The same is true for a PgR modulator mifepristone [33]. Notably, the selective ER-modulator tamoxifen is contraindicated in the treatment of ESS as it has an agonistic activity on endometrial stromal cells.

TARGETED THERAPIES

The immunohistochemical expression of potential therapeutic targets: c-Kit, c-abl, plateled-derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR) in endometrial stromal tumors varied among studies based mostly on single cases or small series. In the largest series investigating potential targets for tyrosine kinase inhibitors (TKI) immunohistochemical or molecular alterations of c-Kit, PDGFRα and EGFR were demonstrated in 2%, 34.6% and 11.5% of ESSs, and in 7.7%, 38.5% and 7.7% of non-LG-EESs, respectively [34]. This study included 52 ESSs and 13 UESs subclassified using the WHO classification.

There are some anecdotal reports of response to c-Kit inhibitor imatinib in disseminated non-LG-ESS and ESS, mainly after chemotherapy failure [35–38]. This includes a case of 8-month regression of c-Kit negative ESS tumor, with strong expression of PDGFR α and β [38].

CONCLUSIONS

Due to rarity of endometrial stromal sarcomas there have been no randomized controlled trials investigating the role of systemic therapies in these tumors in advanced disease setting. Palliative chemotherapy has limited role in non-LG-ESS. Considering both activity and toxicity, doxorubicin or ifosfamide even as monotherapy seems to be the first-line choice in soft tissue sarcomas including non-LG-ESS. Gemcitabine/docetaxel combination provides somewhat higher response rates but at the cost of increased toxicity. Hormonal therapy with progestins, mainly MPA, is an effective long-term palliative management for steroid receptor positive ESS. AIs, particularly letrozole, seem to be also effective as first- and later-line endocrine treatment, and are well tolerated. The role of molecular-targeted therapies in endometrial stromal sarcomas remains to be established.

Conflict of interest

The authors declare that they have no competing interests.

Author's contribution

KS performed literature review and wrote the manuscript, EP participated in literature review and manuscript writing, JJ drafted and reviewed the manuscript. All authors read and approved the final manuscript.

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