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Hormonal therapies in uterine sarcomas, aggressive angiomyxoma, and desmoid-type fibromatosis

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ABSTRACT

We review the role of hormonal therapy in the management of different conjunctive tumors. Progestin and aromatase inhibitors seem active in low-grade endometrial stromal sarcoma, but larger case-series are needed. There is no evidence to support the use of hormonal therapy as an adjuvant treatment for low-grade endometrial stromal sarcoma. We did not find relevant data on the use of hormonal therapy for other uterine sarcomas (e.g., high-grade endometrial sarcoma, undifferentiated uterine sarcoma, and adenosarcoma). Gonadotropin-releasing hormone agonist, anti-estrogens and aromatase inhibitor seem active in advanced aggressive angiomyxoma, but larger studies are warranted. The use of aromatase inhibitor in estrogen-receptor-positive uterine leiomyosarcoma requires further clinical investigation. There is no evidence supporting the use of hormonal therapy in desmoid-type fibromatosis. International collaboration efforts are warranted to better explore the role of hormonal therapies in management of estrogen-receptor-positive uterine leiomyosarcoma, low-grade endometrial stromal sarcoma, and aggressive angiomyxoma.

1. Introduction

Advanced sarcomas are best treated by doxorubicin-based chemotherapy. However, therapeutic interventions, including anti-angiogenic multi-kinase inhibitors, other than chemotherapy could be used (Casali et al., 2018). Some sarcomas or conjunctive tumors are regarded as “hormonal-sensitive”. Data suggests hormonal therapy has therapeutic potential for selected uterine tumors. We aim to summarize available data using systematic research with Medline (last issue 15th May 2019).

2. Uterine sarcomas

About 5% of uterine malignancies are sarcomas. There are 4 predominant forms of uterine sarcomas: leiomyosarcoma (uLMS), low-grade endometrial stromal sarcoma (LGESS), high-grade endometrial stromal sarcoma, and undifferentiated sarcoma. Other histological subtypes are exceptional (e.g., rhabdomyosarcoma or Ewing sarcoma). Malignant Mullerian mixed tumors (e.g., carcinosarcoma) are not considered uterine sarcomas but are dedifferentiated carcinomas with both epithelial and stromal components [Ricci et al., 2017].

2.1. Leiomyosarcoma

2.1.1. Overview

uLMS is the most common uterine sarcoma and accounts for 60% of all uterine sarcomas (Ricci et al., 2017). Some patients are diagnosed after breast cancer treatment with tamoxifen as an adjuvant treatment (Samuji et al., 2013; Botsis et al., 2006; Yildirim et al., 2005; Sabatini et al., 1999; McCluggage et al., 1996). uLMS usually present as a bulky tumor in pre- or post-menopausal women with vaginal bleeding, pelvic or abdominal pain, or abnormal abdominal mass. uLMS usually present as a large well-circumscribed intraluminal mass. Grossly, uLMS contains necrotic, hemorrhagic, and pseudo-cystic structures. uLMS are hypercellular with spindle-shaped or pleomorphic cells showing infiltrative borders and vascular invasion. Morphological variants include epithelioid and myxoid tumors. Distinction between leiomyoma and uLMS is made with conventional morphological criteria (mitosis, atypia, and necrosis). Smooth tumors of undefined malignant potential (STUMP) describes when leiomyoma and leiomyosarcoma cannot be diagnosed with certainty. Large en bloc surgery remains the cornerstone treatment (total hysterectomy with bilateral salpingo-oophorectomy). Radiotherapy seems to reduce the risk of local relapse in large

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tumors but does not improve overall survival. uLMS are associated with poor outcome (5-year overall survival rate is approximately 50%) with a high rate of metastatic relapse (e.g., lung, bone, peritoneum, and liver). Classical first-line treatment of advanced uLMS is based on doxorubicin; nevertheless, other agents are found active (trabectedin, gemcitabine +/- docetaxel, pazopanib, etc.) (Ricci et al., 2017). The role of adjuvant chemotherapy has not been established.

2.1.2. Available data on hormonal therapy in uLMS

Immunohistochemistry analyses revealed that approximately 50% of uLMS express estrogen receptors and progesterone receptors (Comunoglu et al., 2007; Lee et al., 2009; Leitao et al., 2004; Rodriguez et al., 2011). The role of hormonal therapy had been minimally studied with some case-reports (Thanopoulou et al., 2014; Uchida et al., 1996; Altman et al., 2012), 2 retrospective studies (Ioffe et al., 2009, O'Cearbhaill et al., 2010) and 2 phase-2 trials (George et al., 2014; Slomovitz et al., 2018).

A retrospective study of 54 localized uLMS patients treated with surgery revealed that 34 (63%) of tumors were positive for estrogen receptor (ER). ER-positive uLMS tumors had better overall survival (36 months versus 16 months, $p = 0.04$). Four uLMS patients received hormonal therapy as an adjuvant treatment and were free of disease (follow-up: 18–68 months). Eighteen patients received hormonal therapy at the time of recurrence, 14 of which (78%) experienced stable disease or objective response (follow-up: 6–124 months) (Ioffe et al., 2009).

Another retrospective study of 34 patients with advanced or recurrent uLMS treated with aromatase inhibitors revealed 22/31 (71%) and 10/20 (50%) tumors were found to be positive for estrogen receptor and progesterone receptor (PR), respectively. The median progression-free survival with aromatase inhibitors was 3 months (95% CI: 2–5). Overall, the best objective response was 3/34 in unselected patients (9%). The 3 partial responses were noted in ER-positive uLMS, with the durations of treatment being 12.5, 9.5, and 5 months. The one-year overall survival was 2% (95% CI: 11–48) (O'Cearbhaill et al., 2010).

A phase 2 trial assessing letrozole in advanced ER/PR-positive uLMS enrolled 27 patients and 23 tumors (85%) were found positive for estrogen receptor and 4 (15%) were positive for progesterone receptor. Patients received letrozole (2.5 mg/day) for a median time of 2.2 months (range, 0.9–9.9 months). Best responses were stable disease in 14 cases (52%) and progressive disease in 13 cases (48%). There was no confirmed objective response. The 12-week progression-free survival was 50% (95% CI: 36–71). Three patients with uLMS expressing both ER and PR in more than 90% tumor cells received treatment for more than 24 weeks (George et al., 2014).

Regarding these findings, a randomized phase 2 trial assessing letrozole in localized operated uLMS was launched. Unfortunately, only 9 patients were enrolled, with 4 patients receiving letrozole. The 24-month relapse free survival was 100% for patients receiving letrozole and 40% for patients in the observation arm. However due to slow accrual of patients, no formal conclusions could be drawn (Slomovitz et al., 2018).

2.1.3. Synthesis

Despite promising data (O'Cearbhaill et al., 2010; George et al., 2014; Slomovitz et al., 2018), hormonal therapy could neither be recommended as a standard of care in uLMS, nor as a treatment for advanced stages as an adjuvant treatment (level of evidence: IV-D). Further clinical explorations are needed. However, the premature closure of the adjuvant trial (Slomovitz et al., 2018) demonstrates the challenges in conducting clinical trials in selected sarcoma subgroups and suggests that such trials be conducted in international contexts.

2.2. Low-grade endometrial stromal sarcoma

2.2.1. Overview

LGESS represent approximately 15% of uterine sarcomas (Trope et al., 2012). LGESS are diagnosed in women between 40 and 55 years of age. One fourth are asymptomatic. In the remaining cases, common revealing symptoms are vaginal bleeding and pelvic and abdominal pains. Grossly, tumor masses are well defined. Tumor cells resemble endometrial stromal cells. JAZF 1-SUZ 12 rearrangements are common along with other fusions genes (e.g. PHF1-JAZF1, EPC1-PHF1, MEAF6-PHF1, and ZC3H7-BCOR) (Panagopoulos et al., 2008; Panagopoulos et al., 2013). LGESS are regarded as an indolent malignancy and the overall prognosis is good. However, (ultra) late relapses are possible (10–20 years after the initial diagnosis). The median time to relapse in stage I is about 65 months (Chang et al., 1990). Five-year overall survival rate is 90% for stage I-II and 50% for stage III-IV (Chang et al., 1990; Barney et al., 2009). Curative-intent surgery is total hysterectomy and bilateral salpingo-oophorectomy. There is no consensus on the role of ovarian preservation, lymphadectomy, adjuvant radiotherapy, or systemic treatments (Amant et al., 2014).

2.2.2. Hormonal therapy in LGESS

The vast majority of LGESS express both estrogen/progesterone receptors (approximately 70–80%) (Reich et al., 2000; Kurihara et al., 2008; Yoon et al., 2014). Based on case-reports, estrogen replacement therapy and tamoxifen are both contraindicated in cases of LGESS (Pink et al., 2006). Hormonal therapy with progestin or aromatase inhibitor is regarded as the front-line treatment of metastatic or relapsing LGESS. However, regarding the rarity of the disease, only retrospective data are available. About 40 cases of metastatic LGESS treated with progestin have been published. The 3 largest retrospective studies enrolled 8 cases (Chu et al., 2003; Dahhan et al., 2009; Yamazaki et al., 2015). Overall, the reported response is approximately 50% with about 15% of patients experiencing disease progression as the best response (Ioffe et al., 2009; Pink et al., 2006; Chu et al., 2003; Dahhan et al., 2009; Yamazaki et al., 2015; Mizuno et al., 2012). The longest duration of treatment was 180 months (Chu et al., 2003). Less than 50 cases of advanced LGESS treated with aromatase inhibitors have been reported in literature. About 90% of patients experienced clinical benefit, including an objective response in about 2/3 of patients (Altman et al., 2012; Ioffe et al., 2009; Pink et al., 2006; Dahhan et al., 2009; Spano et al., 2003; Ryu et al., 2015; Yamaguchi et al., 2015).

Available data about hormonal therapy as an adjuvant treatment of localized LGESS came from 7 retrospective case series (Chu et al., 2003; Amant et al., 2007; Beck et al., 2012; Cheng et al., 2011; Leath et al., 2007; Malouf et al., 2010; Zhou et al., 2015). Study populations and adjuvant treatment are heterogeneous with conflicting study results and small sample sizes; hence, the statistical robustness of the comparisons was very low. For example, Beck et al. carried out a retrospective study of 43 localized LGESS patients, 16 (37%) recurred with a median time of 100 months (Beck et al., 2012). The rate of relapse was 14% in stage I patients receiving progestins as an adjuvant versus 39% in stage I patients without hormonal therapy (the difference did not reach the level of significance; $p = 0/26$). In the retrospective study by Chu et al., 4/13 patients receiving progestin as an adjuvant recurred compared to 6/9 patients who did not receive adjuvant hormonal therapy (Chu et al., 2003). Leath et al. report that the median overall survival was 94 months for patients receiving progestin as an adjuvant therapy versus 72 months for those without adjuvant hormonal therapy ($p = 0.7$) (Leath et al., 2007).

2.2.3. Synthesis

Aromatase inhibitors and progestins are regarded as standard of care for metastatic LGESS. Though the literature on these therapies is scarce, the data are consistent (level of evidence: III-A). In contrast, literature on hormonal therapy as adjuvant treatment in LGESS is

conflicting.

2.3. Other uterine sarcomas

We did not find relevant data on the role of hormonal therapy in other subtypes of uterine sarcoma: high-grade ESS, undifferentiated uterine sarcoma, and adenosarcoma.

3. Aggressive angiomyxoma

3.1. Overview

This clinic-pathological entity is recent, described first by Steeper and Rosai in 1983 (Steeper and Rosai, 1983). To date, less than 400 cases have been described in English-language literature (Beuran et al., 2017). Cases in men are exceptional (Minagawa et al., 2009). Aggressive angiomyxoma (AAM) occurs in pelvic soft parts, especially in the vagina and vulva (extra-vulvo-vaginal primaries are exceptional: buttock, inguinal or retroperitoneal soft tissue tissues) (Begin et al., 1985; Fetsch et al., 1996; Fucà et al., 2018). Local extension is defined with MRI (Agiro et al., 2015). Diagnosis occurs between 15 and 60 years of age. Tumors are usually slow growing with a cyst-like bulky infiltrating (more rarely pedunculated) mass. Pathological analysis shows myxoid stroma with numerous thin and thick-walled vessels and stellate, diamond-shaped, or spindle cells. Almost all AAM show positive Vimentin and Desmin signals and negative S-100 signals. Large en bloc margin-free resection is considered the treatment of choice. Nevertheless, Fuca et al. have described that among 36 operated patients with aggressive angiomyxoma (including 33 R0/R1 resections), the rate of local relapse was 50%, with a median relapse-free survival of 39 months (Fucà et al., 2018). Management of locally advanced and relapsing aggressive angiomyxoma is challenging.

3.2. Hormonal therapy in aggressive angiomyxoma

Aggressive angiomyxoma is regarded as a hormonal-dependent/sensitive tumor because of female predominance, peak incidence of reproductive age, case-reports of tumor regression after hormonal replacement withdrawal in post-menopaused patients (Agiro et al., 2015). and case reports of tumor growth during pregnancy (Han-Geurts et al., 2006). Several reports show that tumor cells are immune-reactive to both estrogen and progesterone receptors in about 90% of cases (Fetsch et al., 1996; McCluggage et al., 2000; Shinohara et al., 2004; Idrees et al., 2006). Regarding these facts, hormonal therapies have been used for management of aggressive angiomyxoma. We found in literature, first-line treatment is primarily with gonadotropin-releasing hormone (GnRH) agonists (Sereda et al., 2009; Sun and Li, 2010; Schwartz et al., 2014; Aguilar-Frasco et al., 2018). Treatment with aromatase inhibitor (Giles et al., 2008), antiestrogen (Palomba et al., 2011) or their combination (Palomba et al., 2011) is even rare. Reported indications were management of primary huge mass or local relapse not amenable to surgery, neo-adjuvant down-sizing treatment (Sereda et al., 2009; Giles et al., 2008; Palomba et al., 2011) and adjuvant treatment (Sun and Li, 2010; Schwartz et al., 2014; Lee et al., 2011). Schwartz et al. reported a case of aggressive angiomyxoma in a patient with multiple local relapse, treated with re-excision and then adjuvant GnRH agonist for 3 months. At discontinuation of GnRH agonist, the patient experienced local relapse and was treated with GnRH agonist. The re-challenge provided long-lasting tumor control (Schwartz et al., 2014). Literature data are sparse but consistent, suggesting ati-tumoral activity of hormonal therapy. Most of the data came from case-reports. Fuca et al., report a large series of 36 cases. Thirteen patients received a first-line systemic treatment with hormone therapy for locally advanced disease, with an overall response rate of 8/13 (62%) with a median progression-free survival of 24 months (95% CI, 11–40). In two patients, adding an aromatase inhibitor on progression to first-line GnRH agonist resulted in a new tumor response (Fucà et al., 2018). Complete response to GnRH agonist is possible (Shinohara et al., 2004).

3.3. Synthesis

To conclude, aggressive angiomyxoma is a hormone therapy-sensitive tumor; combined treatment with surgery and hormonal therapy is likely the best option. However, the nature (e.g., GnRH agonist alone or combination), the optimal duration and the timing (neo-adjuvant/adjuvant) of the therapy remain unestablished (Level of evidence: IVB).

4. Desmoid-type fibromatosis

4.1. Overview

Desmoid-type fibromatosis (DF, also named desmoid tumor or aggressive fibromatosis) is a rare, locally invasive, non-metastasizing but potentially multifocal proliferation of mesenchymal stem cell progenitors. DF constitutes a soft tissue mass arising at any part of the body, in different types of tissues, including muscle, fascia, and aponeurosis. DF are typically diagnosed in young adults (peak incidence of 30–40 years of age) and mainly in women at reproductive age. The sex ratio of male/female is about 1/6. The tumor is rare. For example, in France (population: 66 million), about 350–400 cases are diagnosed yearly. Histologically, DF are composed of monoclonal spindle-shaped cells separated by an abundant collagenous matrix. The nuclear overexpression of β-catenin is a useful diagnostic tool. There are 2 distinct clinico-biological entities: sporadic aggressive fibromatosis and those associated with Familial Adenomatous Polyposis (FAP, typically associated with intra-abdominal and mesenteric primaries). Both are mutually exclusive, with CTNNB1 somatic mutation in cases of sporadic DF and germline mutation of APC in FAP-associated DF. The outcome of DF is unpredictable; about one third spontaneously regressing, another third spontaneously stabilizing, and one third increasing in size (Penel et al., 2017). Functional impairment and pain are independent to the size change. Today, international recommendations favor wait-and-see policy rather than front-line surgery. Nevertheless, in case of disease progression, systemic treatment could be discussed (Kasper et al., 2017).

4.2. Hormonal therapy and desmoid-type fibromatosis

DF is usually regarded as a hormonal-dependent tumor. However, evidence for this is indirect: female predominance, the peak incidence at reproductive age, the most common primary location of DF is the abdominal wall tumor and many cases of abdominal wall DF are diagnosed within 2 years after pregnancy. There are numerous case-reports of DF increasing in size during pregnancy or regressing with hormonal therapies.

In only three series (of 179 cases), DF were negative for estrogen receptor alpha (Leithner et al., 2005; Deyrup et al., 2006; Santos et al., 2010). Yet, 97 (54%) were found positive for estrogen receptor beta (Leithner et al., 2005; Deyrup et al., 2006; Santos et al., 2010). Hormonal therapies (e.g. GnRH agonist, tamoxifen, toremifene) were used extensively for decades in management of DF in both genders. An overview of these case-reports suggests a partial response rate of about 50% (Bocale et al., 2011). Large retrospective studies provide less enthusiastic data. Libertini et al. have reported a series of 32 patients (including 19 women) treated with tamoxifen in the presence or absence of non-steroidal anti-inflammatory. They report disease progression in 9 cases (28%), stable disease in 22 cases (69%) and partial response in one case (3%) (Libertini et al., 2018). Fiore et al. reported a retrospective series of 44 patients treated with toremifene, with disease progression in 25%, stable disease in 65% and partial response in 10% (Fiore et al., 2015). Additionally, Hansmann et al. reported a retrospective series of 25 patients (including 17 with FAP-associated DT)

treated with sulindac and high-dose tamoxifen (120 mg/day). They report disease progression in 21 cases (84%), stable disease in 2 cases (8%) and partial response in 2 cases (8%) (Hansmann et al., 2004).

Skapek et al. reported the results of a non-randomized phase 2 trial assessing the activity of tamoxifen plus sulindac in children suffering from aggressive fibromatosis (n = 59) (Skapek et al., 2013). This regimen provides disease progression in 44 patients (74%), 10 patients with stable disease (17%), 4 patients with partial response (7%) and 1 (1%) complete response. However, it is well known that spontaneous shrinkage is possible in DF. A recent placebo-controlled randomized phase 3 trial assessing sorafenib in aggressive fibromatosis patients (n = 88) had shown that the rate of objective response under placebo is 20% (Gounder et al., 2018).

Case reports showing regression under hormonal therapy must be interpreted with caution regarding the natural history of the disease (spontaneous regressions are possible). Overview of case-reports, large retrospective cases and one phase-2 trial have reported a response of 50%, 3–10%, and 8%, respectively.

4.3. Synthesis

Hormonal therapy in DF is a popular treatment, but there is no convincing evidence for still prescribing it (Level of evidence IVD). Observed tumor regression with hormonal therapy could be the natural history of DTF.

5. Conclusions

Rare diseases are a challenge to study. Case-reports must be interpreted with caution and prospective and randomized trials are not frequently available. Management of patients remain challenging.

The following conclusions can be drawn: (i) use of aromatase inhibitor in RE-positive uLMS require further clinical investigation, (ii) progestin and aromatase inhibitors seem active in advanced LGESS but larger case-series are welcome, (iii) there is no evidence to support the use of hormonal therapy as an adjuvant treatment in LGESS, (iv) GnRH agonist, anti-estrogen and aromatase inhibitor seem active in advanced aggressive angiomyxoma, but larger studies are needed, and (v) there is no evidence supporting the use of hormonal therapy in desmoid-type fibromatosis.

We strongly recommend international collaborative effort to collect multicenter data and better assess the role of hormonal therapy in uLMS, LGESS, and aggressive angiomyxoma.

Declaration of Competing Interest

None to declare.

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