Case 2 – Adjuvant treatment of high-grade uterine leiomyosarcoma: a still open question

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Abstract
We report a case of localized high-grade uterine leiomyosarcoma treated with surgery after massive bleeding and then with adjuvant chemotherapy with gemcitabine and dacarbazine for six cycles, after multidisciplinary evaluation and discussion with the patient. Adjuvant chemotherapy in uterine sarcomas is still debated, as in all soft-tissue sarcomas, although the risk of recurrence is often high; no adjuvant medical treatment is considered standard since there are no trials demonstrating that adjuvant chemotherapy improves outcome, compared with surgical resection alone. We show that the association of gemcitabine and dacarbazine for six cycles is a feasible adjuvant treatment in this setting, with no relevant side effects.

Key words: adjuvant chemotherapy, soft-tissue sarcoma, uterine leiomyosarcoma

Introduction

Uterine leiomyosarcoma is a rare malignancy with fewer than 2000 cases per year in the United States. Although the majority of women has resectable, uterus-limited disease, patients are at substantial risk for both local and distant recurrent disease. The risks of recurrence for uterus-limited leiomyosarcoma are difficult to ascertain. Retrospective studies have generally included small numbers of patients, reporting recurrence rates ranging from 30% to 80% at 2 or 3 years after diagnosis [1–4]. This high rate of distant recurrence strongly supports the hypothesis of adjuvant chemotherapy in this disease. Among the chemotherapy regimens with evidence of efficacy in metastatic uterine leiomyosarcoma are fixed-dose rate gemcitabine plus docetaxel [5, 6], gemcitabine [7], doxorubicin [8], and ifosfamide [9]. Despite this, a standard chemotherapy regimen in the adjuvant setting does not exist, except for some recent evidence from a phase II study of adjuvant gemcitabine plus docetaxel followed by doxorubicin in patients with high-grade, uterus-limited leiomyosarcoma [10]. We report a case of a 53-year-old female with a diagnosis of high-grade uterine leiomyosarcoma, who underwent surgery at our General Hospital, and was treated with six cycles of adjuvant chemotherapy with the combination of gemcitabine and dacarbazine.

Case presentation

In October 2012, after recurrent metrorrhagia, the patient attended a gynaecological visit and a transvaginal ultrasound showed a diffuse uterine leiomyomatosis (maximum diameter of the largest lesion 6 cm); for the persistent metrorrhagia, a surgical exploration of the uterine cavity was performed with excision of the greater lesion, the pathological diagnosis was high-grade uterine leiomyosarcoma (maximum pathologic diameter 8 cm) [Figure 1 A-D].

In November 2012, the patient underwent hysterectomy and bilateral annessiectomy at our Gynaecologic Oncology Department; the definitive histological examination showed residual expression of high-grade uterine leiomyosarcoma with uterine cervix infiltration and massive necrosis. We performed a pathological review within the Italian Rare Cancer Network that confirmed the diagnosis of high-grade uterine leiomyosarcoma.

In December 2012, the patient underwent a brain, chest and abdominal computed tomography (CT) scan to complete the staging and no secondary lesions were found.

We discussed the patient history in our multidisciplinary gynaecological oncology group – comprising gynaecologic surgeon, pathologist, radiotherapy oncologist and medical oncologist – and we chose to share with the patient the opportunity of adjuvant chemotherapy consider-

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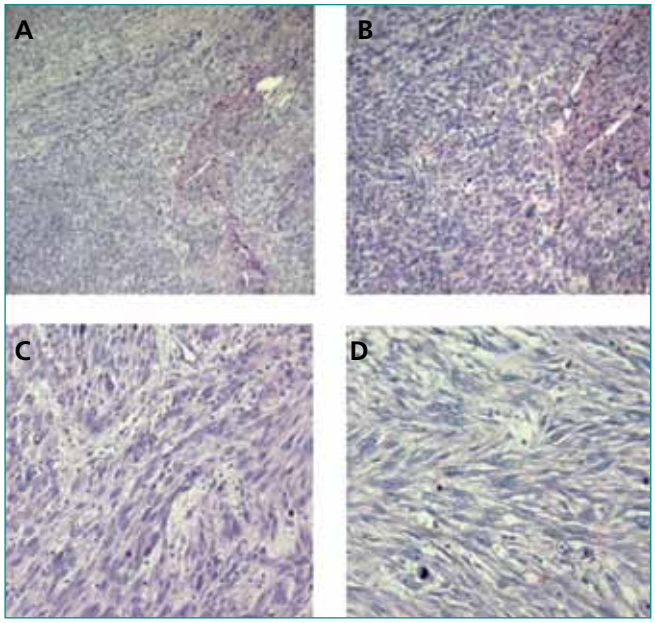

Fig. 1. H&E histopathological aspects of uterine leiomyosarcoma with spindle-cell sorted pattern (A-B), cellular athypia (C) and mytosis (D)

ing the high risk of distant recurrence. We decided not to perform post-operative radiotherapy because it showed no impact in overall survival or local control in prospective studies. When we discussed the option of adjuvant treatment and the possible drugs combination in this setting with the patient, she refused any medical treatment that causes alopecia (e.g. anthracycline-based chemotherapy or docetaxel and gemcitabine) and, therefore, we proposed gemcitabine and dacarbazine, which is an active regimen in the metastatic setting, especially in soft-tissue leiomyosarcomas [10], and the patient accepted.

We placed a central venous line for drug infusion and started chemotherapy in January 2013 with gemcitabine 1800 mg/m^2 (fixed-dose rate 10 mg/m^2/min) and dacarbazine 500 mg/m^2 on day 1 of every 14-day cycle for six cycles until April 2013, and then we started follow-up with a gynaecological visit and CT scan every 3 months.

During treatment, there was no alopecia and no other severe toxicity, except for grade 2 nausea treated with symptomatic drugs and grade 2 thrombocytopenia and grade 3 asymptomatic neutropenia after 4 cycles that required treatment to be delayed. The last chest and abdomen CT scan was performed in December 2013 and no secondary lesions or local recurrences were found.

Conclusion

Adjuvant treatment in uterine leiomyosarcoma is an important medical need and although the risk of recurrence is high, there is no standard strategy in this setting; therefore, the decision should be discussed in a multidisciplinary setting and shared with the patient. In this case report we showed that the combination of gemcitabine and dacarbazine could be safely administered in high-grade uterus-limited leiomyosarcoma. Prospective studies are needed to find out if this regimen improves the outcome of this patients.

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Commentary

Uterine leiomyosarcoma (LMS) represents approximately one third of all uterine sarcomas and is often detected at the time of hysterectomy in women who undergo surgery for a putative leiomyoma. The current standard of care for early stage, completely resected disease is observation. However, the prognosis of this disease is extremely poor, as the probability of relapse is between 50 and 70% [1, 2]. Radiation therapy appears to improve local control in retrospective studies, but has not shown any impact on overall survival. In the EORTC randomized trial of adjuvant whole pelvic radiation versus observation for FIGO stage I and II uterine sarcomas, the recurrence rate was approximately 50% in both arms of the study. The percentage of LMS patients remaining progression-free at 2 years in that study was approximately 58% [3]. The high rate of distant failure in uterine LMS, even in the setting of early-stage disease, provides the rationale for considering adjuvant systemic therapy. Recently, a phase 2 study of adjuvant gemcitabine plus docetaxel followed by doxorubicin in women with localized high-grade uterine LMS conducted by the Sarcoma Alliance for Research through Collaboration (SARC), demonstrated a 2-year progression-free survival (PFS) rate of 78% [4]. This value exceeded historic expectations of 50%. Those observations have led to an international, prospective randomized phase 3 trial currently ongoing in the USA and in Europe. This study compares the adjuvant regimen used in the previous phase 2 study with the current standard of care represented by observation [5]. Unfortunately, this study has faced problems with enrolment. Most likely, the option of eight cycles of chemotherapy versus observation appears unattractive to most patients. Also, the toxicity of these regimens is not marginal. The rationale of using a combination of gemcitabine plus docetaxel and doxorubicin is supported by the activity of these drugs in metastatic uterine leiomyosarcoma [6, 7]. However, although the combination of gemcitabine and docetaxel is a current standard of care in the treatment of advanced disease, the toxicity of this combination is not negligible. Furthermore, the superiority of gemcitabine and docetaxel (which is inactive in leiomyosarcoma when used alone) was not confirmed in a phase 2 study of leiomyosarcoma patients [8]. The combination of gemcitabine (which remains one of the most active drugs in leiomyosarcoma) with dacarbazine (even though the majority reports of activity are limited to its analogue temozolomide) therefore represents a valid alternative. The activity and tolerability of this combination has been demonstrated a few years ago in a randomized phase 2 study which showed superiority of the combination versus dacarbazine alone in soft-tissue sarcomas [9]. Also, in the majority of cases, this combination does not induce alopecia, which may be relevant for a subset of patients. In Italy, a proposal for a phase 2 adjuvant study using gemcitabine in association with dacarbazine in early stage uterine LMS is currently being generated. Adjuvant therapy in uterine LMS is still not considered to be standard treatment, and therefore the choice of therapy needs to be shared with the patient.

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