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Gene Profiling and Therapy: What's the Future? A Case Report of Uterine Leiomyosarcoma

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Abstract

Background: Uterine leiomyosarcomas (uLMS), although rare (3%-7% of all uterine malignancies), represent an important share of mortality due to uterine pathology. Surgery is the cornerstone of treatment but the lack of data from randomized clinical trials makes the function of adjuvant therapy still nebulous. For these reasons, the treatment of the uLMS is still a challenge in progress.

Case presentation: We report the case of 72-years old woman who underwent several lines of therapy. After systemic disease progression, was subjected to a genetic test that showed a mutation of CDKN2A. Basing on these results, the patient started Palbociclib, which is still ongoing.

Conclusion: The choice of drug was based on the presence of the patient's specific mutation and not on therapeutic options recommended by guidelines. In this woman, heavily pretreated, Palbociclib showed the stability of disease at the first re-evaluation with an acceptable safety profile and no signs of cumulative toxicity.

Keywords: Uterine ; Hysterectomy; Ovary

Introduction

Uterine leiomyosarcomas (uLMS), arising from the myometrium, represent the most common type of uterine sarcoma, with poor prognosis. They account for approximately 3%-7% of all uterine malignancies [1] and are characterized by an early hematogenous spread and a high rate of distant metastasis, located especially in lungs, even in the absence of lymph nodes involvement [2,3].

Metastatic disease diagnosis is often delayed and made after hysterectomy. The definition of a clear therapeutic approach is limited by the rarity of the disease and, consequently, the lack of randomized studies. Hysterectomy is currently the therapeutic cornerstone. Adjuvant radiotherapy seems to have had an advantage in the local control but not in the OS [4].

Also, the role of systemic therapy is not well defined, although it is still used for the high tendency to relapse, that it stands around 50%-70% [5].

As in other diseases, the final aim of uLMS treatment is to find molecular targets for new potential drugs [6].

The most frequent mutation found in uLMS are growth factors over-expression as C-MYC, Bcl-2, K-ras, and Ki-67, and loses in tumor suppressors as p16, p53, Rb1, ING2 and D14S267 [6]. However, multiple genetic aberrations and very complex karyotypes make difficult to identify molecular targets and can facilitate the refractoriness to subsequently treatment lines.

In this context, where traditional therapies turned out to be ineffective, a new approach resulted in fundamental.

We present the case of a heavily pre-treated metastatic uLMS patient that, because of previous lines failure and not tolerated side effects, underwent DNA sequencing, to evaluate a targeted therapy.

Case Presentation

This is the case of a 72 years old patient, with a previous non-oncological history of arterial hypertension, bronchial asthma, and hypercholesterolemia.

A pelvic mass was shown in December 2008 and she was subjected to histeroannessectomy.

Histological examination revealed a leiomyosarcoma of the uterine wall with epithelioid aspects, a maximum diameter of 4.7 cm and a mitotic index>10/10 HPF. Vascular invasion and metastasis were present in the right ovary.

From February 2009 to July of the same year, six cycles of Doxorubicin 50 mg/mq and Ifosfamide 5 g/mq, as adjuvant systemic therapy, were administered. Then regular follow-ups were performed.

In October 2012 a CT scan demonstrated multiple pulmonary metastases and 2 cm left breast nodular lesion correlated to uLMS. Therefore, it was started a second line chemotherapy with Gemcitabine 900 mg/mq 1°, 8° and Docetaxel 100 mg/mq 8° q21 with poor response, so in March 2013 this treatment was stopped, and a new-one Trabectedin based was started (Trabectedin 1.7 mg/mq q21).

The CT scan performed in October 2013 showed the stability of all lesions except one, localized in the apical segment of the LID. The

patient underwent right inferior pulmonary lobectomy surgery and synchronous removal of the left breast nodule. Histological examination confirmed the uterine nature of the lesions.

After surgery, she continued Trabectedin 1.7 mg/mq q21 until February 2016, when, because of further pulmonary progression, she began chemotherapy with Paclitaxel 80 mg/mq 1°, 8°,15°q28 .

From May 2016 to May 2017, for further progression, she underwent chemotherapy based, in order, on Pazopanib 800 mg die, pegylated liposomal Doxorubicin 50 mg/mq 1°, q28 and Vinorelbine 30 mg/mq 1°-8° and Gemcitabine 800 mg/mq 1°-8° q21, always with pulmonary progression.

In November 2017, after detection of brain metastasis, she began therapy with Temozolomide 150 mg/mq with a failure with this therapy too, showed by the CT scan of February 2018.

At the same time, a genetic test by sequencing DNA and RNA was performed.

On the base of this evaluation, revealing a CDKN2A mutation, a therapy with CDK4/6 inhibitor was began and is still ongoing.

The imaging evaluation performed by CT scans, after two and four months, showed stable disease, with any relevant side effects.

Discussion

Although uterine sarcomas are rare diseases and represent less than 3% of uterine neoplasms, with an incidence of 0.36 per 100,000 woman-years [7], they play an important role in cancer-related death [8].

Their intrinsic biological aggressiveness often associated with a delayed diagnosis, lead to early metastasizing and resistance to therapy; complete responses do not exceed 8% [6].

Despite the process of carcinogenesis is not defined in detail, it has been remarked the molecular instability of this neoplasia, resulting from several genetic errors [9].

Although the role of chemotherapy is not clearly defined yet, especially due to the rarity of the disease, it is generally administered, for locally and at distance relapse high rate.

Generally, a regimen containing single agent doxorubicin or gemcitabine/docetaxel or doxorubicin/olaratumab is preferred for high-grade uterine sarcomas, for both relatively good response rate and favorable toxicity profile.

Aromatase inhibitors could be considered for low-grade ER/PR-expressing uLMS [10]. A general overview of the main therapies recommended by the National Comprehensive Cancer Network (NCCN) is shown in Table 1.

However, as in the case of our clinical case, patients face different lines of therapy, often without satisfying response.

Preferred Therapies	Other Combination Regimens	Other Single-Agent Options	Other Hormone Therapies
Doxorubicin	Doxorubicin/ifosfamide	Dacarbazine	For Low-grade ESS or Hormone Receptor Positive (ER/PR) uLMS
Docetaxel/gemcitabine	Doxorubicin/dacarbazine	Gemcitabine	Megestrol acetate (category 2B for ER/PR positive uLMS)
Doxorubicin/olaratumb	Gemcitabine/dacarbazie	Epirubicin	Medroxyprogesterone acetate (category 2B for ER/PR positive uLMS)
Aromatase inhibitors for low-grade ESS	Gemcitabine/vinorelbine	Ifosfamide	Aromatase inhibitors (for ER/PR positive uLMS)
		Liposomal doxorubicin	GnRH analogs (category 2B for low-grade ESS and ER/PR positive uLMS)
		Pazopanib	
		Temozolomide	
		Trabectedin	
		Eribulin (category 2B)	
		Vinorelbine (category 2B)	
		Docetaxel (category 3)	

Table 1: Systemic therapy for uterine sarcoma (NCCN guidelines Version 2.2018).

Data about Progression-Free Survival (PFS) of our patient compared with those reported in the literature are summarized in Figure 1. As showed, our patient had the most benefit from the Trabectedin therapy, with stable disease for more than two years, except for the growth of a pulmonary nodule, surgically removed. The other therapies did not exceed 5 months of PFS. The patient suffered from relevant toxicities, especially after taxanes and anthracyclines chemotherapies.

In this context, genetic aberrations study could offer an additional opportunity to better understand the disease.

Genetic tests used are based on the extraction and sequencing of tumor DNA and RNA from histological samples, like a biopsy or surgical specimen, in order to identify the detectable genetic mutations, targetable with authorized oncology drugs or used in on-going clinical trials.

In this patient, the test used showed a CDKN2A mutation. In a US study it was found that about 19% of the evaluated 279 samples with advanced/recurrent uLMS, had mutations of the Cyclin-Dependent Kinase (CDK) pathway, and CDKN2A mutations, inactivating p16INK4a, were identified in 11% of uLMS [11].

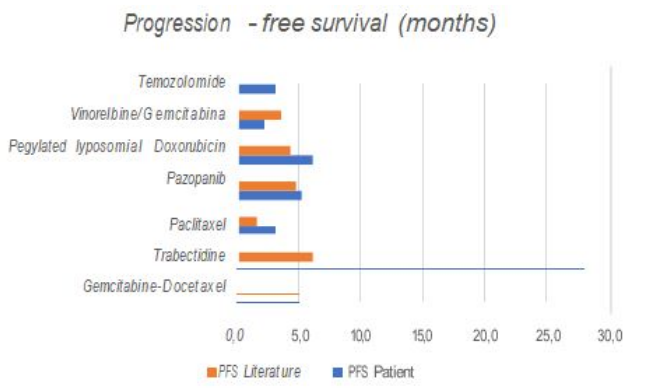

Figure 1: Progression free survival in our patient compared to literature's ones.

CDKN2A is the acronym for cyclin-dependent kinase Inhibitor 2A, a gene located on chromosome 9 band p21.3, ubiquitously expressed in many tissues and cells and coding for several proteins, including two oncosuppressor protein, p16INK4a and/or p14ARF. The first one is involved in binding CDK4 and CDK6 cyclins, preventing them from playing their role as a cell progression stimulator. The p14ARF instead prevents p53 degradation, which is probably the most important protein in cell cycle regulation [12].

Loss of p16INK4a and/or p14ARF has been associated with poor prognosis in several soft tissue sarcomas, including leiomyosarcoma [13] and a statistically significant correlation has been shown between decreased expression of p16 and large tumor size in some tissue sarcoma [13].

The report of the genetic evaluation provides information about trials currently active for the mutations found. Specifically, four trials were reported, three of which were phase II. Two of these trials investigate Palbociclib use. The other ones are focused on Ilorasertib.

Based on these data, therapy with CDK4/6 inhibitor was started, which is actually on-going, with stable disease [14,15].

Conclusion

It is undeniable that the panorama of medicine is actually changing. The diagnosis of cancer has become dynamic and the therapeutic process has constantly expanded, due to the large improvement of diagnostic procedures, such as genomic and proteomic profiling, anatomical and functional imaging techniques, treatment modalities too. Spatial and temporal heterogeneity of solid tumors is not fully understood by the main instruments in our hands. A complex disease characterization is growing up and requires "tailored" treatments taking into account also patient's quality of life and preferences. It is desirable that predictive models could be added for the management of this rare disease, such as uterine sarcomas. Multimodal information could help clinicians choosing the most appropriate treatment, obviously in a multidisciplinary scenario.

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