

The Role of Monoclonal Antibody Targeted Therapy in Uterine Sarcomas

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The uterine sarcoma is one of the type of neoplasm that affects the abdominopelvine organs. The behaviour of this histopathological type of cellular line is very aggressive both to the primer organ and also to the nearby organs and to the main filter' organs like the liver and lung, where it develops metastasis. The treatment of this disease is multidisciplinary and it uses many therapeutic strategies depending on staging and the other comorbidities of the patient. We will present the case of an 81 year old female known with the diagnosis of relapse tumoral abdominopelvin sarcoma developed one year after total hysterectomy surgery with bilateral anexetomie for the uterine sarcoma. Also we will discuss about a series of characteristics of the treatment plan observed at different similar cases. We will evaluate the latest drug lines used in oncology treatment, we will discuss about the therapeutic indications and in the end we will draw conclusions about the therapeutic indications of each case.

Keywords: abdomino-pelvin tumors, sarcoma, multidisciplinary

Sarcomas are rare malignant tumors, being more common in the pediatric population [1]. The sarcoma classification includes more than 100 histological subtypes, [2] but in this paper we will refer to uterine sarcoma, our attention being directed to leiomyosarcoma.

Uterine sarcomas are tumors of the soft tissues derived from mesenchymal cells, and are tumors with a high degree of aggression, with frequent loco-regional and metastasis to distant organs. The high degree of recurrence, regardless of the stage of the disease at the time of diagnosis, is still a common denominator of sarcomas [3]. The most common types of uterine sarcoma are well and less differentiated endometrial tumors, undifferentiated uterine sarcomas and leiomyosarcomas. Rarely, adenosarcomas and uterine rhabdomyosarcomas can be found in medical practice [4].

Uterine leiomyosarcomas are malignant tumors that develop from myometric cell aberrant mitosis. They typically reach large dimensions (greater than 10 cm) [5], with areas of necrosis and haemorrhage being present at a high frequency. The tumor presents estrogen and progesterone receptors, [6] which allows the use of hormonal drugs in the therapeutic scheme of this pathology. The diagnosis of certainty is usually posthysterectomy or following a myomectomy in case of a leiomyoma suspicion. Clinically, the patient may experience postmenopausal bleeding, abnormal bleeding in premenopause, abdominal pain, bloating, urological manifestations, or in a few cases it may be asymptomatic. Biomorphologic tests are necessary, but imaging (ultrasound, tomography, magnetic resonance) shows extra information about the presence of a tumor and details of localization, homogeneity and consistency, the relationship with the surrounding organs, the extension of neoplasia, the latter being of real use in establishing the therapeutic plan [7]. The relationship with the surrounding organs generally refers to the cavitous and parenchymatous organs, but may also include the bony pelvis, if local invasion occurs; the surgical management of these invasions includes wide excision and reconstruction with grafted bone or metallic augments, often necessitating the use of state-of-the art techniques

like 3D reconstruction and 3D printing, which were developed for hip and knee reconstructive surgery [8-12].

Experimental part

Case presentation

We present the case of an 81-year-old woman known to be diagnosed with abdominopelvin tumor. The patient is admitted for specific symptomatology related to an intestinal occlusion: slowed intestinal transit for faecal matter, emetised status, inappetence, tegumentary pallor, and increase abdominal volume predominantly in the inferior floor. The patient is dispensarised (taken under surveillance sau hospitalized) through the general practitioner for the following diagnoses: fast-onset atrial fibrillation, essential arterial hypertension, senile dementia, straight breast cancer for which radical mastectomy with axillary lymphadenectomy was practiced about eight years ago, total hysterectomy with bilateral annexectomy by classical approach done one year ago - median pubo-supraumbilical laparotomy that was practiced in another hospital unit for the diagnosis of uterine sarcoma and the result of the anatomopathological bulletin was: the tumor consisting of fusiform cells with intersected fusion cells with high cell density, nucleus with prominent nuclei, mitoses present, thickened blood vessels - aspects strongly suggestive of a sarcoma-like proliferation. After the intervention, the patient performed twelve chemotherapy treatments according to the following regimen: administration of Docetaxel Endovenous Infusion at three weeks postoperatively and Gemcitabine endovenous infusion starting with day one as well as day eight, a cure consists of Docetaxel + Gemcitabine on day one and Gemcitabine may additionally be given on day eight, and the cycle was repeated on day twenty one. Six standard cycles were performed, hence twelve chemotherapy treatments.

Post-chemotherapy the situation was stable until the resurgence of the locoregional evolution of neoplastic disease. The main modified biomorphic constants worth mentioning which influenced the patient's postoperative evolution were: leucocytes 11,580 / microlitres (normal

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values 3.39-8.86), hemoglobin 10.3g / dL (NV 11.1-14.7), serum sodium 132mmol / L (NV 136-146), glucose 122 mg / dL (NV 74-106), 20 µg / dL sideremia (NV 60-180). The patient is subjected to a toraco-abdominal-pelvic nuclear magnetic resonance scan with a contrasting substance indicating the following: uterus is not visualized - surgically ablated; a non-homogeneous tumor formation with a 10 cm diameter cranio-caudal diameter / 9.2 centimeters antero-posterior / 8 centimeters axial to the pelvis on the right side of the pelvis (fig. 1).

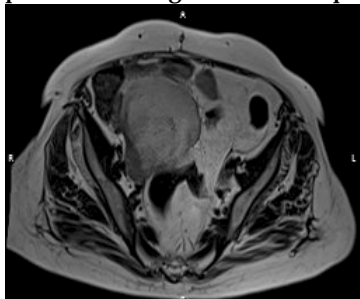


Fig. 1. Abdominal-pelvic image from the patient's contrast MRI

The tumor formation is situated at the back of the rectosigmoid junction which it invades, on the sides comes in contact with the right external iliac vessels, with the ileo-spasus on the right side and on the upper side with the enteral mass invading two ileals in the middle portion of the ileum (fig. 2). The right ureter shows a posterior tract of the tumor, is compressed without being invaded by the tumor.

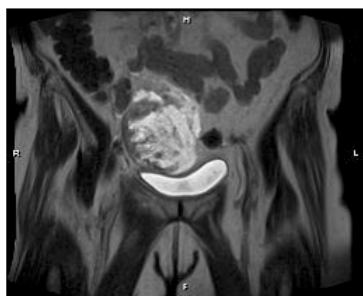


Fig. 2. Abdominal-pelvic image from the patient's contrast MRI

Colonoscopically, the presence of a tumor with extrinsic development is present which also invades the upper rectal mucosa and fixes the rectum wall without being able to be mobilized performing colonoscopic maneuvers. Serial biopsies are collected, establishing the following histological diagnosis: a tumor formation consisting of fusiform cells disposed in intersecting bundles with high cell density, nucleus with prominent nuclei, mitosis present - aspects suggestive of a sarcomatous proliferation. Given the identical microscopic appearance of these biopsies, we consider that this tumor is a sarcoma tumor recurrent after a uterine sarcoma.

During the hospitalization, a hydroelectrolytic and metabolic rebalancing treatment is instituted aiming at the normalization of the biomorphic constants, the cardiologic state is re-evaluated and the cardiologic treatment is readjusted by resorting to intravenous drugs. The close monitoring of the cardiac function both in pre-op as well as in post-op care is of significant impact to the outcome of the procedure, and is becoming ever-more complex as new methods of evaluating the outcome of therapeutic procedures in cardiac disfunctions are developing [13]. After normalization, or in some cases the improvement of the biohumoral constants, and achievement of a favorable psychological status, surgery is performed. Under general anesthesia with orotracheal intubation, a pubosupombilical medial iterative laparotomy is undertaken. It is difficult to get access to the peritoneal cavity due to multiple adhesions. Intraoperatively, an approximately 14/12/10 centimeter tumorous oval shape

is seen, with abdominopelvin location, imprecisely delimited invading the rectosigmoid junction, with several intestinal aneurals in the middle portion of the small intestine, as well as the abdominopelvin peritoneum corresponding to the internal opening of the inguinal canal and the adjacent tissue of this region. The tumor formation, along with the invasive structures, are isolated and the excision of the tumor formation takes place, extensive mandatory enterectomy with laterolateral mechanical ileoil anastomosis, rectosigmoid resection with the distal rectal catarrh, and the proximal endus exodosis in the left iliac anus, the resection of the parietal peritoneum and adjacent connective tissue.

Results and discussions

Immediately after the intervention the patient is admitted to the Intensive Care Unit where she receives specialized treatment. Two days after surgery the patient's general condition is good, hemodynamic and respiratory stable, reasons for which the patient is transferred to the normal unit. On the forth postoperative day, the evolution is set back by an agitated psychomotor status with a tendency to aggression and distortion of reality, exacerbated symptomatology on the background of senile dementia and voluntary suppression of medication. With the resumption of intestinal transit, the patient is given preponderantly liquid foods and is then diversified until food intake is normalized. There are difficulties in mobilizing the patient both because of the advanced age and because of the occurrence of a chronic algic syndrome manifested in the internal side of the left thigh. Discharge is performed on day ten after surgery when the patient is in good condition considering the age, stage of disease and other medical conditions. For this therapeutic stage we consider the case as a success, long-term evolution being influenced by multiple factors. Approximately thirty days after the surgery, the histologic diagnosis of the tumoral cell is established (fig. 3), as it is a tumor recurrence of uterine sarcoma for which total hysterectomy with bilateral anexectomy was practiced one year ago.

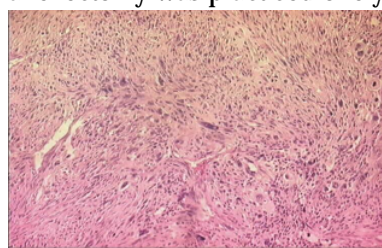


Fig.3. Histologic diagnosis of the tumoral cells

Therapeutic plan in uterine sarcoma

The treatment plan for uterine sarcomas is adapted depending on the stage of the disease, the current therapeutic strategies being based on treating the patient rather than the disease. Neoplastic pathologies can not benefit from a correct and effective therapeutic attitude in the absence of imaging. Initially, when there is suspicion of a pelvic tumor on the basis of patient's symptoms and bio-humoral investigations, it is recommended to perform a thoraco-abdomino-pelvic computerized tomographic scan with contrast agent to assess the location, size and consistency tumor, relationships with surrounding tissues, or distant extension [14]. Magnetic Resonance and PET-CT are imaging investigations that add extra features to describing neoplasia. These methods are also recommended in case of local relapse or residual posthysterectomy abnormalities [15, 16]. In the case of giant uterine sarcomas that are located unilaterally the patient may present gait abnormalities, with an exacerbation of pre-existing musculoskeletal conditions such as arthrosis,

which may be dealt with at a later time in accordance with current protocols, [17-19] or plantar fasciitis and calcaneal spurs, considered a clinical manifestation of pre-existing plantar arch collapse and gait disfunction, which in turn has several treatment options [20-22]. A critical moment is the determination of the histopathological type of the tumor and the degree of dysplasia by histopathological examination. Depending on this diagnosis, which is both the diagnosis of certainty and modern imaging, we can place the patient at a stage of evolution of the disease and establish an appropriate treatment plan according to the latest therapeutic guidelines [23]. In this paper we focused on the treatment of uterine leiomyomas to be categorized and staged as follows, in accordance with the TNM/FIGO Classification [4] (tables 1-4).

The degree of differentiation of leiomyosarcomas

G1 - Well-differentiated

G2 - Moderately-differentiated

G3 - Poorly-differentiated

G4 - Dedifferentiated

Surveillance of patients diagnosed with uterine sarcoma in one of the above-mentioned therapeutic lines implies: [23, 24].

- Repeat biopsy with histopathological examination every 3-4 months for 2-3 years, then every 6-12 months

- Educating patients about the symptoms of a possible relapse.

Local recurrences in a patient who did not follow radiotherapy require either immediate administration of these in combination with brachytherapy or systemic therapy, or surgery with resection and radiotherapy together with postoperative systemic therapy [25]. If the patient has received radiotherapy before, resection laparotomy with resection or systemic therapy is required.

Detecting metastasis during surveillance is influenced by the therapeutic approach. The patient will either continue systemic therapy and radiotherapy in case of unresectable metastases, or be directed to a surgical site for ablation of the secondary tumor. In the first case, the patient may have a secondary indication of the response to systemic therapy. When opting for the first phase for metastatic ablation, this should not exclude continued systemic therapy and postoperative.

Table 1
T- PRIMARY TUMOR

TNM	FIGO	Surgical-Pathologic Findings
Categories	Stages	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to the cervix (disregard extension to the corpus)
T1a	IA	Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread
T1a2	IA2	Measured stromal invasion > 3.0 mm and ≤ 5.0 mm with a horizontal spread ≤ 7.0 mm
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T1b2	IB2	Clinically visible lesion > 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T2a2	IIA2	Clinically visible lesion > 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctional kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctional kidney
T4	IV	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)
T4a	IVA	Tumor invades mucosa of bladder or rectum (bullous edema is not sufficient to classify a tumor as T4)
T4b	IVB	Tumor extends beyond true pelvis

Table 2
N - REGIONAL LYMPH NODES

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Table 3
M - DISTANT METASTASIS

M0	No distant metastasis
M1	Distant metastasis (including peritoneal spread; involvement of supraclavicular, mediastinal, or para-aortic lymph nodes; and lung, liver, or bone)

Table 4
STAGE GROUPING

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB	T1b	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T1, T2, T3a	N1	M0
	T3b	Any N	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

The results obtained recommend the realization of interdisciplinary research for the use of robotic biointerfaces [26-28].

The current chemotherapy treatment:

At this moment, the recommend and trustworthy therapeutic regiments are:

- sistemic therapy with doxorubicin a with or without olaratumab or gemcitabine
- inhibitors of aromataza for the well defined tumours

Antracicline

In this group is doxorubicin. Studies had shown that combined with olaratumab it gives better chances of survival in faze II of randomisation. Antraciclin binds directly to DNA, inhibiting synthesis and fragmentation of DNA. It metabolises in the liver and it excrets through bile in to the digestive tract but also through urine as an active metabolite. Doxorubin is administered as an intravenous infusion, with constant medical observation both during and after administration.

Clareance:

- infants and children younger than 2 years = 813 mL/min/square meter
- children older than 2 years and teenagers = 1540 mL/min/square meter
- adults = 324 to 809 mL/min/square meter (higher for males)

The systemic clearance is semnificant smaller for the obese patients.

Side effects: cardiotoxicity (atrio-ventricular block, bradycardia, arterial or ventricular extrasistols, depolarisation changes, heart failure), hair loss, pruritus, amenorrhea, abdominal pain, hyperuricemia, anorexia, gastrointestinal ulcer, leukopenia, neuropenia, anemia, trombocytopenia and changes in the colour of the tear, saliva and sweat secretions.

Pazopanib

Pazopanib is a selective inhibitor of tirozin kinaza that blocks the tumoral development and angiogenesis. It acts on the receptor for vascular grown factor, platelet and fibroblast. Among the side effects we mention: nausea, vomiting, diarrhea, loss of appetite, hyperglycaemia, high blood pressure, hypocalcemia, hypomagnesemia, hypokalemia, proteinnuria, hair lose, abdominal pain, increase of transaminases, myelosuppression. The risk of liver failure is low, but there were reported sever cases of liver failure.

The mechanism of action: the tirozin kinaza inhibitors limits tumor development by inhibiting the VRGF-2, VEGFR-2, VEGFR-3(vascular endothelial grown factor), pdgfr-alpha and beta(platelet-derived growth factor), FGFR-1, FGFR-3 factors, the cytokine receptors, IL- receptors.

Pharmacodynamics:

- proteine binding more than 99%
- liver metabolism
- the bioavailability increases with food ingestion and decreases when fragmented
- in case of liver damage is recommended to lower the doses

Olaratumab

Olaratumab is a recombined human monoclonal antibody used with antracicline in the treatment of the advanced stages of soft tissue sarcoma. The action mechanism of olaratumab consists in binding and blocking the alpha receptor of the growth factor derived from platelets(PDGFR-alpha). the receptor is located in many neoplastic tissues, like sarcoma. At this level is involved in

cell growth and differentiation, its activation causing cellular proliferation and distant metastasis. The treatment with olaratumab implies that the tumor has no indication for surgery nor radiotherapy.

The gastrointestinal toxicity consists in ; nausea, vomiting, diarrhea and abdominal pain when administered in combination with doxorubicin in compared to the mono therapy with doxorubicin.

The liver toxicity consistsn in lymphopenia stage 3-4, neutropenia and thrombocytopenia, more severe in dual therapy.

Side effects: fatigue, hair loss, hipoglycemia, nausea, lymphocytopenia, musculoskeletal pain and increase of alkaline phosphatase.

Conclusions

As shown in the presentation we can tell that the uterine sarcoma is an aggressive form of oncological disease, with an unfavourable evolution both through the speed of extension and also through the fact that it affects women all ages and no matter of the hormonal status. The complexity of treating this disease is caused by the many factors involved in the establishment of a medical conduct. A very important fact is represented by the stage of the disease, in other words the time passed from the beginning of the illness to the moment of diagnostic. Most of the time the symptoms that lead the pacient to a medical consult are the symptoms given by the extension of the disease, even the presence of metastases and their extension and because of this the treatment is mostly palliative. Another fact that is very important in the success of the treatment is the interdisciplinary cooperation of the medical team. Considering the many therapeutic resources and the fast acces to the latest medical discoveries we consider that the best approach is an aggressive one but only in the best interest of the patient, in other words we recommend a full hysterectomy with bilateral anexectomy and radical limfadenectomy, full resection of the tumor, the resection of the metastases and oncological therapy and radiotherapy. In order to have the best results we must not forget that prevention is the key to success. And if we talk about prevention, in case of minimal invasive treatment of uterine tumours believed to be benign, we have a risk to influence in a bad way the evolution of the sarcoma with uterine starting point when we perform a robotic or laparoscopy procedure that needs to use the morcellator.

About 5% of these tumors considered first to be benign turned out to be different types of cancer and in the case of intraabdominal morcellation the consequences can be serious from two points of view: the destruction of the specimen which leads to the impossibility of a correct staging and the distance inseminatin that involves a very bad prognosis because of the fast metastases and the tumor recurrence.

In the end, we recommend to plan interest groups for the genital pathology of sarcoma origin, that includes different specialities like oncology, radiotherapy, gynaecology, general surgery, thoracic surgery, orthopedics, gastroenterology, pathological anatomy and imagistics.

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