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Case Report

Long-Term Control of Metastatic Myxoid Liposarcoma of the Thigh with Palliative Trabectedin: A Case Report

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Abstract

We would like to present the case of a 61-year-old patient with liposarcoma who experienced prolonged stabilization of the disease by palliative treatment with trabectedin after several relapses from previous lines of treatment. After the initial diagnosis of liposarcoma of the left thigh, standard treatment protocols of isolated limb perfusion with tumor necrosis factor and melphalan, surgery and subsequent adjuvant radiotherapy were performed, resulting in a disease-free period of approximately seven years. Eight years after the initial diagnosis, a solitary metastasis was seen in the right femoral iliac fossa. Therefore, we indicated and performed preoperative combined radio-chemotherapy with high-dose ifosfamide due to the progression-free survival of more than 7 years. Preoperative restaging by PET/CT and MRI showed a response of the treated metastasis in the right femoral iliac fossa, but new multiple osseous metastases, thus a palliative situation was present. We decided not to perform the metastasectomy as initially planned but to follow a watch-and-wait strategy. Progression of multiple metastases was not evident until 11 months after the end of combined radio-chemotherapy, so then the indication for palliative systemic therapy was given. After rebiopsy, the histological examination showed parts of a myxoid liposarcoma only, round cell parts were not seen. So we recommended and carried out therapy with trabectedin. This achieved a partial remission that could be maintained for about 18 months. After progression on trabectedin, a tumor resection was performed in the right pelvic region and a four-month trabectedin break was given. A renewed challenge with trabectedin resulted again in stable disease.

Keywords: Trabectedin; Alkylating agent; Adipose tissue neoplasm; Myxoid liposarcoma; Metastatic; Palliative treatment

Introduction

Liposarcoma, although a rare disease with an estimated incidence of 2.5 cases per million inhabitants, is the most commonly diagnosed adult sarcoma [1]. It is a neoplasm occurring in the adipose tissue, mostly located in the deep tissues of the thigh [2]. Myxoid liposarcomas, representing 30-40% of all liposarcomas in the limbs, are the second-most common type of liposarcoma after the well-differentiated subtype [3,4]. Typically, the patients suffer from swelling, numbness, and a decreased range of motion, but also general symptoms such as fatigue, weight loss or gastric disturbances, which may vary depending on the location. Many patients, however, remain symptom-free until the tumor is large and impedes adjacent tissues [5].

The mainstay of treatment of localized disease is surgery, while irradiation may be a valuable adjunct to improve local

control. However, myxoid liposarcoma has a propensity to relapse, despite appropriate treatment of local disease [2]. Systemic therapy is limited to metastatic disease and there is a range of therapeutic options. The value of neoadjuvant and adjuvant therapy is still unclear [2,6]. The rate of 5-year survival in patients with myxoid liposarcoma was recently estimated at 76.4% to 88.2% [3].

Here we present the case of a patient with myxoid liposarcoma of the left thigh who had relapsed from tumor necrosis factor alpha (TNF-α) and melphalan, surgery, radio-chemotherapy with high-dose ifosfamide, and palliative radiotherapy and surgical removal of metastases, and subsequently received trabectedin in this palliative setting.

Case Presentation

We present the case of a now 61-year-old male patient who was 49 years old in August 2010, the time of initial diagnosis of myxoid liposarcoma of the left thigh. Figure 1 shows an overview of all diagnostic and therapeutic measures and their results over time.

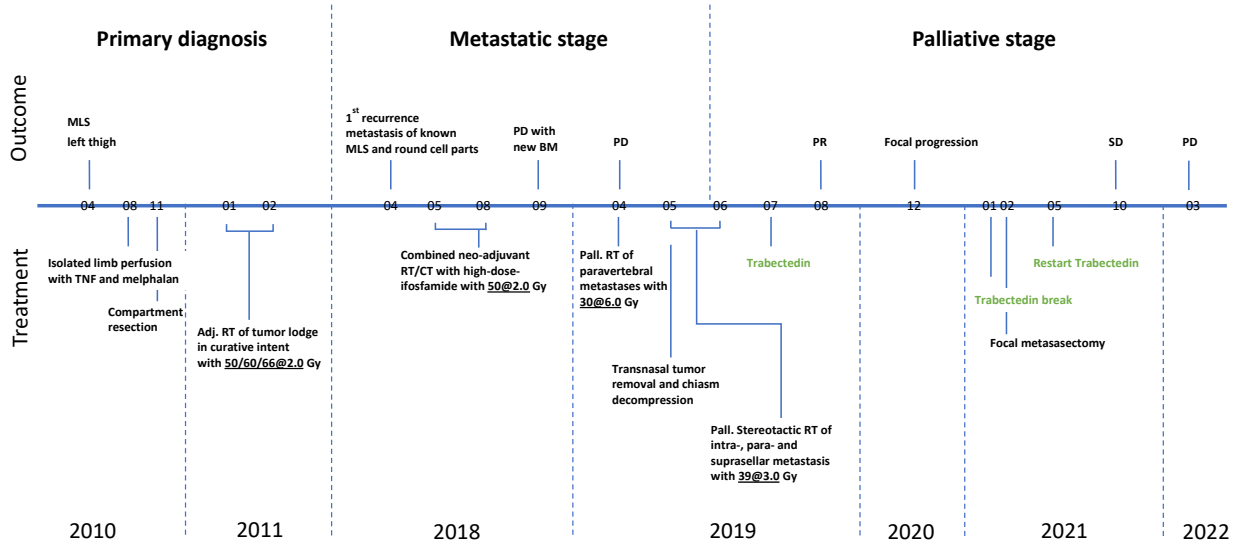

Figure 1: Overview of diagnostic and therapeutic measures and outcomes over time. Adj: Adjuvant; BM: Bone metastasis; CT: Chemotherapy; MLS: Myxoid Liposarcoma; Pall: Palliative; PD: Progressive Disease; PR: Partial Remission; RT: Radiotherapy; SD: Stable Disease

Initial diagnosis

After initial diagnosis, the patient received an isolated limb perfusion with TNF-α and melphalan. The thoracoabdominal staging computed tomography (CT) showed no signs of metastases. Subsequently, the patient underwent compartment resection of the dorsal left thigh, followed by adjuvant radiotherapy in curative intent, resulting in a disease-free period of approximately seven years.

Metastatic stage

In April 2018, the patient had a first solitary metastasis, presenting in the CT as a 10 x 6.9 cm mass isodense to soft tissue containing cystic parts in the right pelvis, which extended into the obturator foramen and with displacement of the prostate and urinary bladder and infiltration of the internal obturator muscle biopsy revealed a metastasis of the known myxoid liposarcoma with focal transition into round cell parts. The fluorescence in-situ hybridization (FISH) detected a rearrangement of the DNA damage-inducible transcript 3 (DDIT3, also known as C/EBP homologous protein [CHOP]) in 68% of the counted cells in the break-apart sample. Staging by positron emission tomography (PET)-CT was conducted and no further distant metastases were evident. The metastatic lesion itself measuring approximately 10 x 8 cm showed a heterogeneously hypermetabolic and lobulated tumor mass in the right pelvis with extension through the right obturator foramen and infiltration of the internal obturator muscle. There was diffusely increased ^{18}F-fluorodeoxyglucose (FDG) activity in the adjacent os pubis without definite morphologic changes or cortical erosion.

In the presence of a solitary metastasis, a progression-free-survival (PFS) of more than 7 years and a good general condition of the patient, we indicated and performed a preoperative combined radio-chemotherapy with high-dose ifosfamide.

Palliative stage

In September 2018, restaging after the end of combined radio-chemotherapy by PET/CT showed a response of the metastasis decreasing to a size of about 8 x 6 x 6 cm and unchanged tumorous infiltration of the nearby pelvic ring on the right side, but pelvic MRI showed an additional osseous metastasis. Therefore, we performed a whole-body MRI and saw multiple osseous metastases, thus a palliative situation was present.

With the exception of the right pelvic metastasis, all lesions were rather small and posed no threat to stability. We decided therefore not to perform metastasectomy of the metastasis in the right femoral iliac fossa since it had already been treated and there was a response, but to follow a watch-and-wait strategy. In case of local progression at any other site, local radiotherapy would be performed.

In March 2019, a whole-body MRI was performed, which showed a progression of a soft tissue nodule between the quadratus lumborum muscle and the psoas major muscle on the left. In addition, a further lesion suspicious for metastasis was discovered in the lumbar spine (lumbar vertebra 2).

In April 2019, palliative radiotherapy of progressive paravertebral metastases on the left side as well as in the lumbar vertebra area 2 with 30 Gy each (5 x 6.0 Gy) was performed.

In late April 2019, the patient reported visual disturbance with double vision and visual field loss. A subsequent cranial MRI showed an intra-, para-, and suprasellar metastasis with infiltration of the orbit, with contrast enhancement and likely infiltration of the optic chiasm, as well as bilateral infiltration of the cavernous sinus and infiltration of the pituitary gland and pituitary stalk, which were new compared with the 2018 MRI.

In May 2019, a transnasal micro-navigated transsphenoidal tumor removal and decompression of the chiasm were performed. Histologic evaluation of the tumor specimen showed portions of a prediagnosed myxoid liposarcoma. Palliative stereotactic radiotherapy of the intra-, para-, and suprasellar metastatic lesion was performed with 13 fractions of 3.0 Gy between May and June 2019.

Palliative systemic therapy with trabectedin

Progression of multiple metastases was not evident until 11 months after the end of combined radio-chemotherapy, so the indication for palliative systemic therapy was given. After the biopsy, the histological evaluation showed parts of a myxoid liposarcoma only, round cell parts were not seen. Therefore, in July 2019 we began a therapy with trabectedin at 1.5 mg/m^2 24h intravenous infusion once every three weeks. From the 4th cycle onwards, only 85% of the standard dose was administered due to side effects (gastrointestinal symptoms and pronounced fatigue); from the 15th cycle onwards, trabectedin was administered once every 6 weeks as a maintenance therapy. The patient received a total of 33 cycles. Systemic treatment was well tolerated with side effects not exceeding grade 1. This treatment resulted in partial remission (Figure 2), which was maintained for about 18 months. Figure 2 shows magnetic resonance imaging (MRI) images of the period between December 2018 and April 2020.

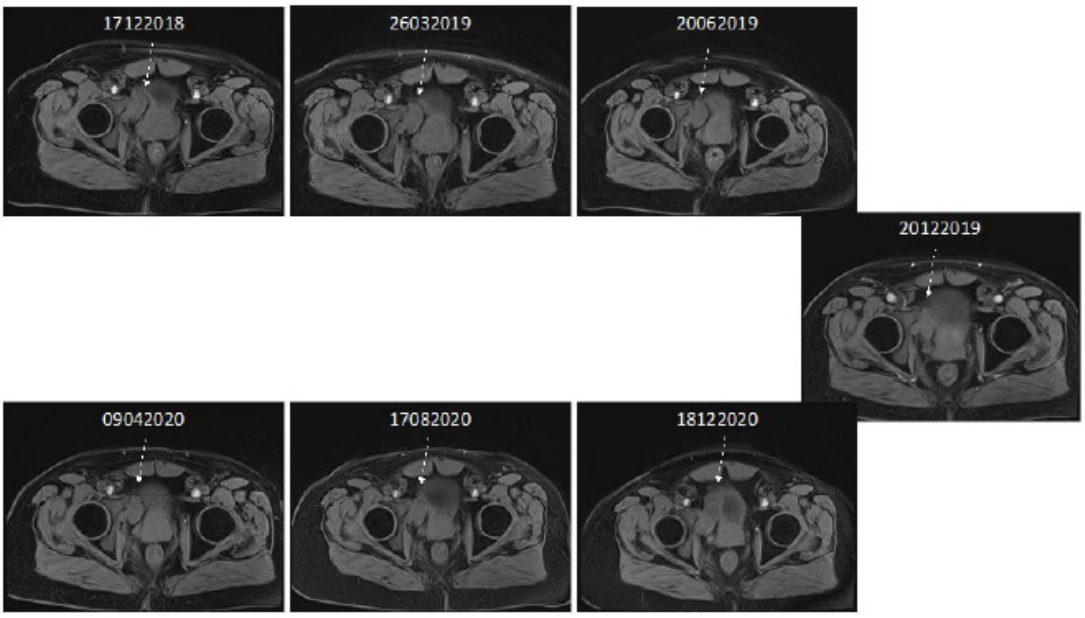

Figure 2: MRI images over the course of the metastatic and palliative stages.

In December 2020, whole-body MRI showed progressive disease with progression of the known right pelvic metastasis. Otherwise, there were multiple, avital osseous metastases of the axial and limb skeleton unchanged and no new osseous metastases were visible. Therapy with trabectedin was paused and resection of the right iliac metastasis with resection of the obturator nerve was performed in February 2021. Histology of the resectate consisting of two nodules showed that one nodule (image morphologically size stationary) corresponded to a vital metastasis of the known myxoid liposarcoma without round cell parts and with a maximum diameter of 4.1 cm. The other node (image morphologically size progressive) was completely devitalized, as if pedunculated, corresponding to an infarcted tumor portion, with a maximum diameter of 5.3 cm. The resection was classified as R2 according to the clinical indication, as there was tumor extension into the bone which was deliberately not removed. Retrospectively, there was no tumor progression because the image-morphologically size-progressed portion of the nodule was avital tumor tissue. Postoperatively, complicating iliac lymphocele and infected seroma occurred, so we could not continue palliative systemic therapy until May 2021. Therapy with trabectedin was continued until March 2022, followed by a switch of palliative systemic therapy to eribulin upon further tumor progression. The patient received 6 cycles of eribulin, after which exacerbation of pain occurred and the treatment was stopped to initiate adequate pain medication. After two months of treatment break, tumor progression was diagnosed and pegylated liposomal doxorubicin hydrochloride was initiated and maintained until to date.

Discussion

We show the case of a patient with myxoid liposarcoma with multiple osseous metastases treated with trabectedin in the palliative setting who achieved long lasting disease stabilization. From initial diagnosis to detection of the myxoid liposarcoma on the left thigh and subsequent compartment resection and adjuvant radiotherapy of the tumor lodge in curative intent, the patient had a progression-free period of seven years. Five months after the detection of a first solitary metastasis, osseous metastases were diagnosed, after which the patient quickly deteriorated into palliative stage. It is known that metastatic myxoid liposarcoma, especially when disseminated skeletal metastasis is involved, is associated with worse outcomes [3,7]. Despite this difficult situation, the patient's disease could be stabilized for more than 4 years using trabectedin, an alkylating agent with antitumor activity related to its blockade of tumor DNA repair mechanisms, which inhibits cell proliferation and induces apoptosis, as well as the modulation of the cytokines and chemokines in the tumor microenvironment [8-10].

Myxoid/round-cell liposarcoma can be accurately diagnosed by its hallmark genetic translocation t(12:16)(q13:p11) or more rarely the translocation t(12;22)(q13;q12) [11]. The common t(12:16)(q13:p11) translocation produces the chimeric fusion protein FUS-CHOP (or DDIT3-TLS), which binds to specific DNA promotors that eventually lead to malignant tissue transformation [12]. Trabectedin inactivates the FUS-CHOP oncogene and causes its detachment from targeted DNA promotors [13]. Research has

shown that two of the three most commonly occurring chimera of FUS-CHOP [14] (fusion of exon 7 [type 1] or exon 5 [type 2] of FUS to exon 2 of CHOP) respond to trabectedin, while the type 3 [exon 8 of FUS to exon 2 of CHOP] does not [13,15]. Regular CHOP is induced by different types of noxious stimuli, such as DNA damage and endoplasmatic reticulum stress. Consequently, the normal differentiation program is paused or even inhibited, which triggers apoptotic processes to eliminate the damaged cells. When FUS is fused to CHOP, these processes are altered and lipogenic terminal differentiation programs are inactivated eventually causing myxoid liposarcoma [13]. It is hypothesized that trabectedin, through its DNA binding capabilities, might displace the fusion of CHOP and FUS by competition, which leads to the elimination of the chimera from the targeted promotors and eventually to their degradation [13]. These mechanisms may explain the extraordinary chemosensitivity of myxoid liposarcoma to trabectedin.

The presented patient demonstrated substantially longer progression-free survival (PFS) than previously seen in clinical trials of trabectedin in soft tissue sarcomas [16], where the longest observed median PFS was 16.1 months (95% CI 5.5-21.9) in a phase III trial of first-line therapy in translocation-related soft tissue sarcoma [17]. In a long-term single-center experience with 32 advanced and pretreated myxoid liposarcomas patients receiving trabectedin [18], therapy could be stopped in almost one-third of patients (10/32) in the absence of any evident disease, mostly after complete surgery of residual lesions. In these 10 patients, PFS was 28.1 months (95% CI 25.6-36.4; range 12.0-36.4) at a median follow-up of 25 months from treatment start [18]. In the total population of 32 patients, the median PFS was 17 months (95% CI 13.5-30.1), and median overall survival was not reached at the time of analysis. In the present case, trabectedin allowed a progression-free survival of 30 months.

Conclusions

Even in progressive and metastatic disease of myxoid liposarcoma, trabectedin treatment may lead to long lasting stable disease and should therefore be taken into account in palliative treatment.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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