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Metastatic Liposarcoma: A Case of Partial Remission with Eribulin in Late Treatment Lines

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Abstract

Liposarcoma, a type of soft tissue sarcoma, represents a therapeutic challenge, in particular in the metastatic setting. This case describes a patient with retroperitoneal liposarcoma that was first treated by surgery and, upon manifestation of metastatic disease, with a series of chemotherapy regimens comprising doxorubicin (line 1), doxorubicin plus ifosfamide (line 2), trabectedin (lines 3 and 4) and dacarbazine (line 5). While transient partial remission was achieved in the first three lines, rapid disease progression was observed in subsequent therapies. After failure of the previous chemotherapy regimens, eribulin was administered (line 6), and partial remission was achieved within five months. However, the occurrence of grade 3 polyneuropathy led to temporary discontinuation of therapy. Overall, metastatic liposarcoma was controlled for twelve months with eribulin treatment in a heavily pre-treated patient. This case underscores the efficacy of eribulin in treatment-refractory advanced/metastatic liposarcoma.

Keywords: Liposarcoma; Retroperitoneum; Metastatic; Chemotherapy; Eribulin

Introduction

Liposarcoma is a soft tissue sarcoma that originates from adipocytic cells. This cancer can occur in various parts of the body, often the limbs, the trunk or the retroperitoneum. Liposarcoma is biologically heterogeneous and relatively uncommon, accounting for less than 1% of cancers [1]. Hence, the set of effective treatment options is limited, in particular in the metastatic setting. The standard first-line chemotherapeutic option in metastatic liposarcoma is anthracycline-based, either alone or in combination with ifosfamide or olaratumab. A number of different drugs are emerging as subsequent therapeutic options [2-4]. One such drug is eribulin mesylate (eribulin), which has been used to treat metastatic breast cancer for a number of years. In 2016, eribulin was approved in various regions of the world for the treatment of liposarcoma. This approval is based on the favourable results of a phase-III study, which showed a clinically relevant benefit of eribulin in liposarcoma patients in terms of overall survival (OS) and also progression-free survival (PFS) [5,6]. Eribulin is indicated for treatment of unresectable liposarcoma in patients who have received prior anthracycline-containing therapy.

Real-world evidence for effectiveness of eribulin in liposarcoma is still sparse. This case report describes a liposarcoma patient with partial remission under eribulin after failure of various prior chemotherapy regimens. A timeline of the case is displayed in Figure 1.

Case Report

A 28-year-old woman presented with unspecific abdominal pain. Based on computed tomography (CT) scans and a CT-guided biopsy, a myxoid/round cell liposarcoma of the retroperitoneum was diagnosed. The tumour was of stage pT2b (deep tumour extending > 5 cm) without nodal involvement or metastases and was moderately differentiated (grade G3). There were no therapeutically relevant comorbidities except for hypothyroidism. The tumour was removed by surgery (R1 resection). Respecting the patient's preference, no adjuvant measures were applied.

However, peritoneal metastases were discovered one year later. These were treated by partial peritonectomy combined with a single dose of doxorubicin, applied via hyperthermic intraperitoneal chemotherapy (HIPEC). The disease progressed nine months after treatment, resulting in intra-abdominal metastases in the lower pelvis, which were not amenable to surgery. Instead, second-line chemotherapy was conducted with a combination of doxorubicin (75 mg/m²/course) and ifosfamide (10 g/m²/course) for a total of four months. A long-lasting partial remission was achieved.

Nonetheless, abdominal and peritoneal progression was noted after eleven months. Therefore, third-line chemotherapy with trabectedin (1.5 g/m²/course) was initiated, which achieved another partial remission. Due to the clinical benefit, maintenance chemotherapy with trabectedin was administered. The treatment had to be discontinued after eight months because of severe fatigue (CTCAE grade 3).

Two months later, the disease progressed at the same metastatic sites. Dose-reduced trabectedin (1.2 g/m²/course) was instigated as fourth-line chemotherapy. With this exposure, progressive disease was observed as best response to treatment within two months. Due to the ineffectiveness of trabectedin, fifth-line chemotherapy with dacarbazine was started. Again, treatment failure with progressive disease was observed within two months. Thus, multiple chemotherapeutic treatment options had failed.

At this stage, the recently approved treatment option eribulin was employed as sixth-line chemotherapeutic agent. Contrary to the situation in the two previous lines, treatment with eribulin resulted in partial remission within five months (Refer the CT scans in Figure 1). However, a severe adverse drug reaction (ADR) developed: polyneuropathy (PNP) of CTCAE grade 3. PNP was consecutively managed with duloxetine and amitriptyline combined with dronabinol. Ultimately, eribulin therapy had to be discontinued due to PNP after five months. After cessation of eribulin treatment, the patient recovered

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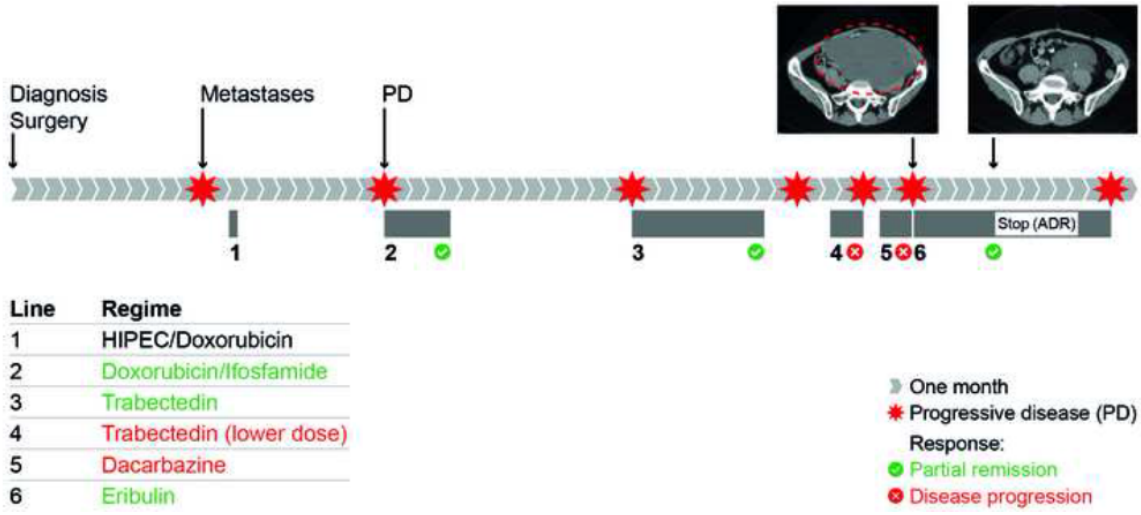

Abbreviations: ADR: Adverse Drug Reaction; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; PD: Progressive Disease.

Figure 1: Timeline of the case featuring major events, chemotherapy regimens with their respective outcome, and computed tomography (CT) scans taken at the indicated times.

from PNP, which was reduced to grade 1 within two months and completely disappeared within an additional three months. Progressive disease was noted during the pause, and re-exposure to eribulin was considered appropriate. As a pre-emptive measure, intermittent alpha-lipoic acid and permanent duloxetine were given in parallel to eribulin. Indeed, treatment-emergent PNP could be prevented, but disease progression was detected after two months, leading to treatment discontinuation. In total, eribulin treatment in sixth line achieved a disease control for twelve months, underscoring its therapeutic activity and potential use in earlier lines in liposarcoma.

Discussion

This case report describes a heavily pre-treated liposarcoma patient with bulky disease who achieved a long-lasting partial remission to eribulin treatment. This supports the principle effectiveness of eribulin even at such an advanced stage. Strikingly, eribulin administration led to (transient) tumour shrinkage even though such remission was seen only rarely in the pivotal clinical trial [6].

The outcome of advanced/metastatic liposarcoma is typically poor, with a median OS of less than two years [4]. The rapid disease progression under dacarbazine is in line with the aggressive nature of this disease and underscores the clinical relevance of an appropriate individualised therapy, which may lead to superior survival in patients.

It is elusive for what biological reason eribulin was effective in this case while the prior regimens were not. It is likely that unknown patient-individual factors played a role. Further, it is conceivable that a resistance mechanism to some of the prior chemotherapy regimens (i.e., doxorubicin, ifosfamide, trabectedin, dacarbazine) might have enriched sarcoma cells that were responsive to eribulin. There is still little knowledge of resistance mechanisms in liposarcoma since the condition is rare and some of the treatment options (such as eribulin) have been introduced only recently. More information on resistance mechanisms and potential biomarkers would be helpful for clinicians to choose the right chemotherapeutic agent in a more systematic manner. The case presented here clearly shows the importance of choosing the right chemotherapeutic agent in this setting, and that only one or few of them may be effective.

The various agents that are available for the treatment of liposarcoma differ in their modes of action. Eribulin is a unique microtubule-targeting agent that affects microtubule polymerisation and sequesters tubulin into non-productive aggregates [7,8]. Eribulin is primarily anti-mitotic but has been suggested to impact the tumour microenvironment and to induce vascular remodelling as well [1,8]. Such effects might have contributed to the benefit seen with eribulin in this case.

The effectiveness of eribulin was however accompanied by severe PNP, a known ADR of eribulin [7]. In the phase-III clinical trial, peripheral sensory neuropathy of all grades affected 21% of liposarcoma patients treated with eribulin [6]. In breast cancer, PNP of all grades was observed in 27.4% [9] and 35% [10] of patients under eribulin and was the most common ADR leading to discontinuation of eribulin treatment, in 3.4% of patient [10]. Here, PNP was reversible and was successfully prevented upon re-exposure to eribulin. Despite the successful supportive measure, re-exposure to eribulin lacked clinical efficacy. It is unlikely that the co-medication of eribulin with duloxetine and liponic acid impaired clinical efficacy as no interaction has been reported for this combination so far. In addition, pharmacokinetics do not support interactive potential: While duloxetine and liponic acid rely on hepatic metabolism, eribulin predominantly undergoes biliary excretion, is not metabolised in the human body and is not a substrate for CYP3A4, underlined by a lack of interaction with ketoconazole or rifampicin [7].

To the authors' knowledge, this is the first case report describing efficacy of eribulin in liposarcoma in late lines of palliative chemotherapy. However, cases of eribulin efficacy in later lines have occasionally been described in other cancer entities: Long-lasting control or partial remission could be achieved with eribulin in some heavily pre-treated patients suffering from other types of sarcoma [11,12] or breast cancer [13,14].

The case described here suggests that eribulin represents a

treatment option in liposarcoma patients where chemotherapy with other agents is not efficacious. In addition to the pivotal clinical trial [6], this case is further evidence to support recent recommendations from Japanese authors [15], who advise to treat metastatic liposarcoma with doxorubicin first and to consider trabectedin and eribulin afterwards. Guidelines for the management of soft tissue sarcomas that do not feature eribulin yet [4] should be updated accordingly.

Conclusion

Treatment with eribulin can achieve partial remission in patients with advanced/metastatic liposarcoma after several other chemotherapeutic options have failed. Hence, eribulin should be considered as a therapeutic option in liposarcoma and warrants testing in earlier therapeutic settings.

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Conflict of Interest

VG: has received honoraria from Lilly, Eisai and PharmaMar for lectures.

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